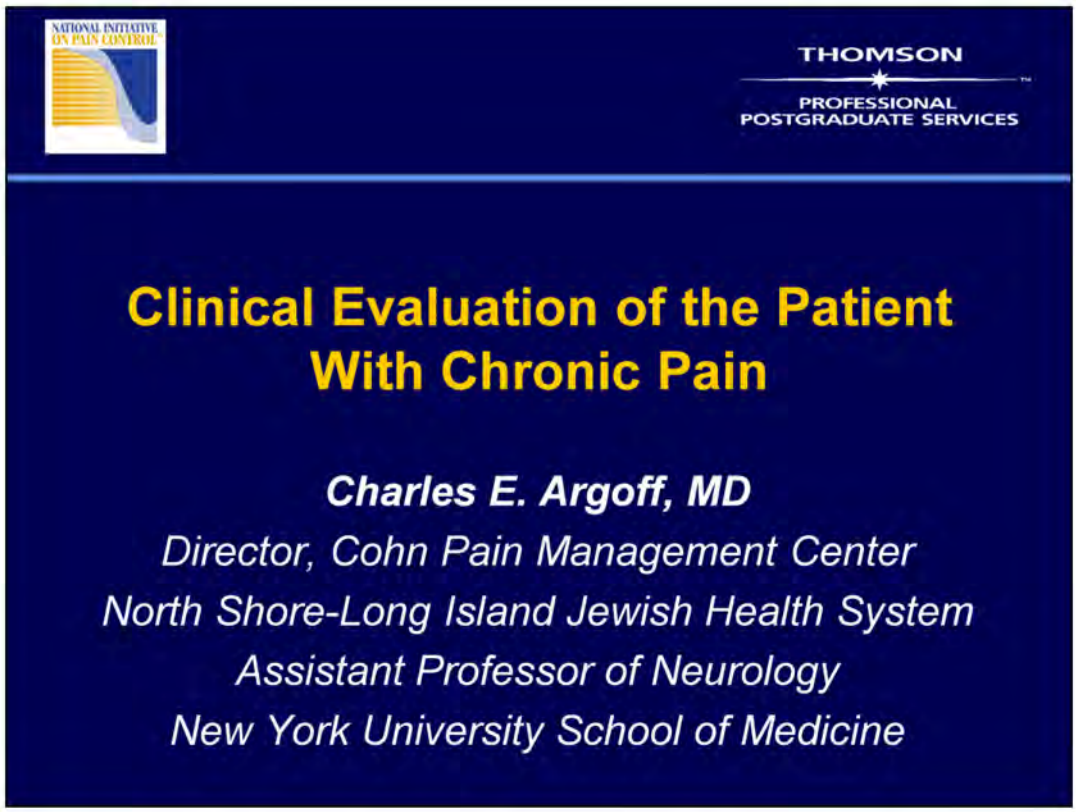
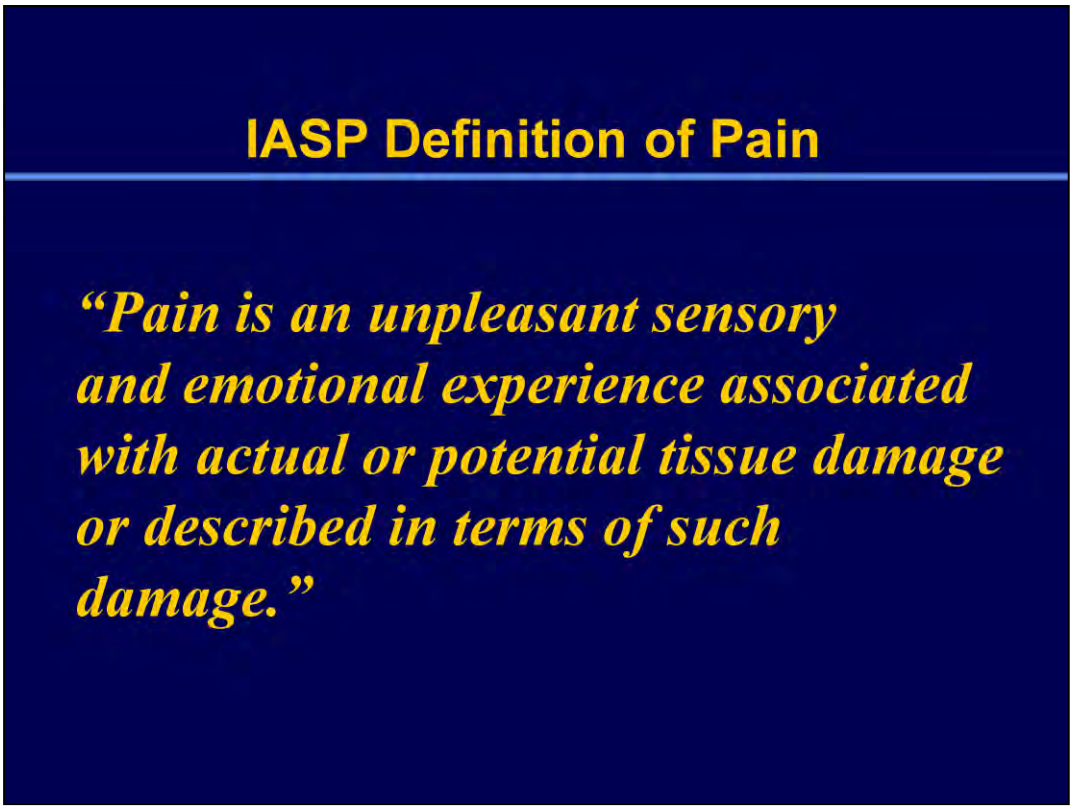
PSJ2 Exh 2


NATIONAL INITIATIVE ON PAIN CONTROL
THOMSON
PROFESSIONAL POSTGRADUATE SERVICES
Clinical Evaluation of the Patient With Chronic Pain
Charles E. Argoff, MD
Director, Cohn Pain Management Center
North Shore-Long Island Jewish Health System
Assistant Professor of Neurology
New York University School of Medicine



- Because of the inherent subjective nature of pain, and the fact that the word "pain" itself connotes multiple meanings, the International Association for the Study of Pain (IASP) has established a standardized definition of pain.
- The definition makes several important points:
  - Pain is an unpleasant emotional experience as well as an unpleasant sensory experience. This distinction between the sensory aspects of pain and its emotional (or affective) component has had a significant influence on both research and the treatment of chronic pain.
  - Also emphasized by the IASP in its definition of pain is that pain is always subjective. If patients regard their experience as pain and if they report it in the same ways as pain caused by tissue damage, it should be accepted as pain.

IASP Task Force on Taxonomy. In: Merskey H, Bogduk N, eds. *Classification of Chronic Pain*. 2nd ed. Seattle, Wash: IASP Press; 1994:209-214.

Chronic Pain Is Expensive

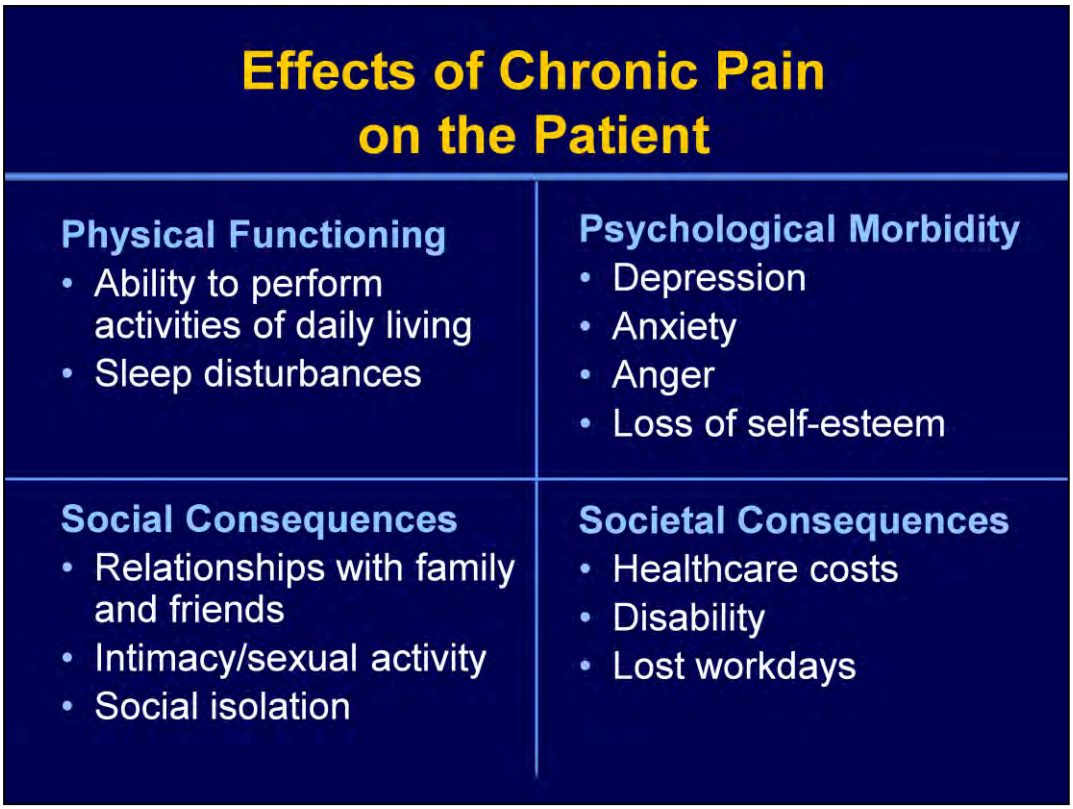
- Chronic pain disables more people than cancer or heart disease and costs the American people more than both conditions combined.
- Pain problems total $70 billion a year in medical costs, lost working days, and workers' compensation.

Acute vs Chronic Pain

Characteristic	Acute Pain	Chronic Pain
Cause	Generally known	Often unknown
Duration of pain	Short, well-characterized	Persists after healing, ≥3 mo
Treatment approach	Underlying disease	Underlying disease and pain disorder

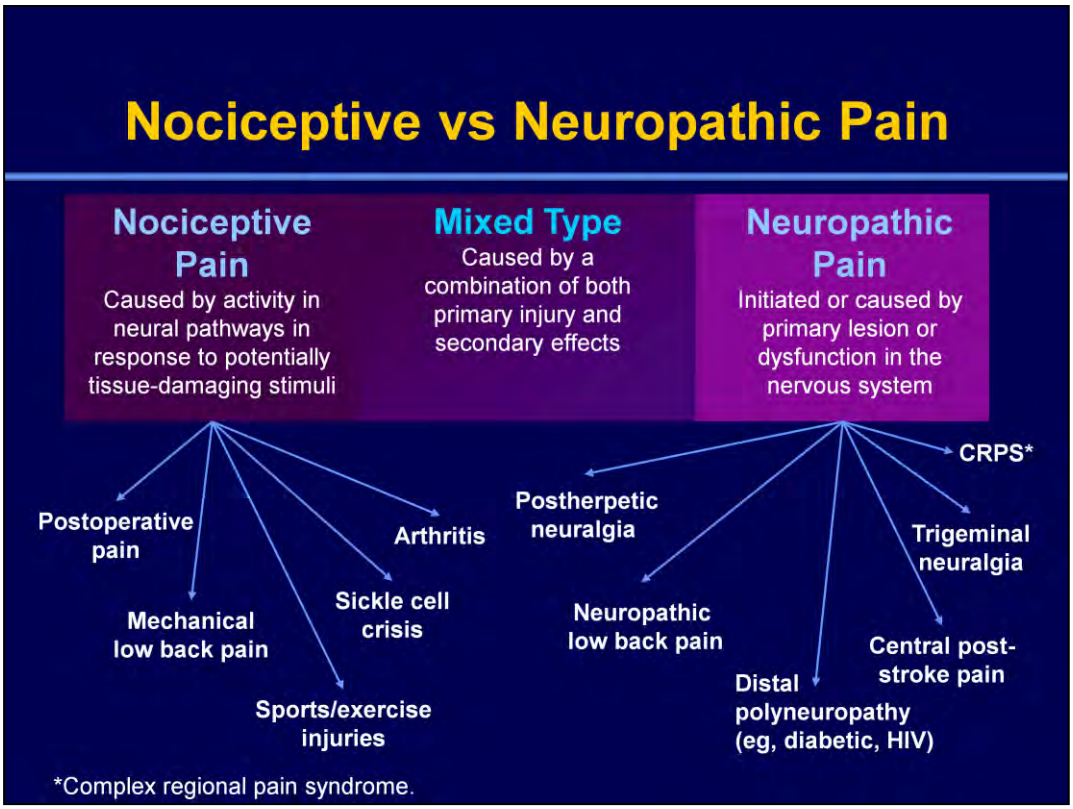
- The causes of acute pain are often known, but the causes of chronic pain and its associated symptoms are not well understood.[1]
- The pain experienced by patients with acute pain often can be alleviated. In general, the duration of acute pain is brief and has been well characterized.[1] The time course of chronic pain, however, is usually indeterminate, and this type of pain is often refractory to treatment.[2]
- One definition of chronic pain is pain that has persisted beyond the time of normal healing; for research purposes, however, chronic pain is often defined as pain that has persisted at least 3 (sometimes 6) months.[3]
- Because chronic pain can almost never be cured,[4] optimal treatment usually involves helping the patient restore function and supporting a patient's coping by utilizing approaches that minimize pain, maximize quality of life (QOL), improve sleep, and enable patients to return to work and perform their regular activities.[3,4]

1. Galer BS, Dworkin RH. *A Clinical Guide to Neuropathic Pain*. Minneapolis, Minn: The McGraw-Hill Companies, Inc; 2000:7-8.
2. Rowbotham MC. Chronic pain: from theory to practical management. *Neurology*. 1995;45(suppl 9):S5-S10.
3. Portenoy RK, Kanner RM. Definition and assessment of pain. In: Portenoy RK, Kanner RM, eds. *Pain Management: Theory and Practice*. Philadelphia, Pa: FA Davis Company. 1996:6.
4. Woolf CJ, Mannion RJ. Neuropathic pain: aetiology, symptoms, mechanisms, and management. *Lancet*. 1999;353:1959-1964.



- Living with chronic pain has been demonstrated to have deleterious effects on many aspects of the patient's daily life. These effects include deterioration in physical functioning, the development of psychological distress and psychiatric disorder, and impairments in interpersonal functioning.[1] For example, approximately 40% of patients with chronic pain also experience major depression.[1]
- The interpersonal consequences of chronic pain are also clear. Marriages and other family relationships may suffer when an individual who is in pain is not able to be active in the relationship or feels depressed or anxious. Intimacy is not usually discussed in patient-physician relations, but intimacy in a relationship can change dramatically when a partner has chronic pain.[2]
- In addition to the personal suffering it causes, chronic pain imposes a burden on society in increased healthcare costs, disability, and lost workdays.[1]

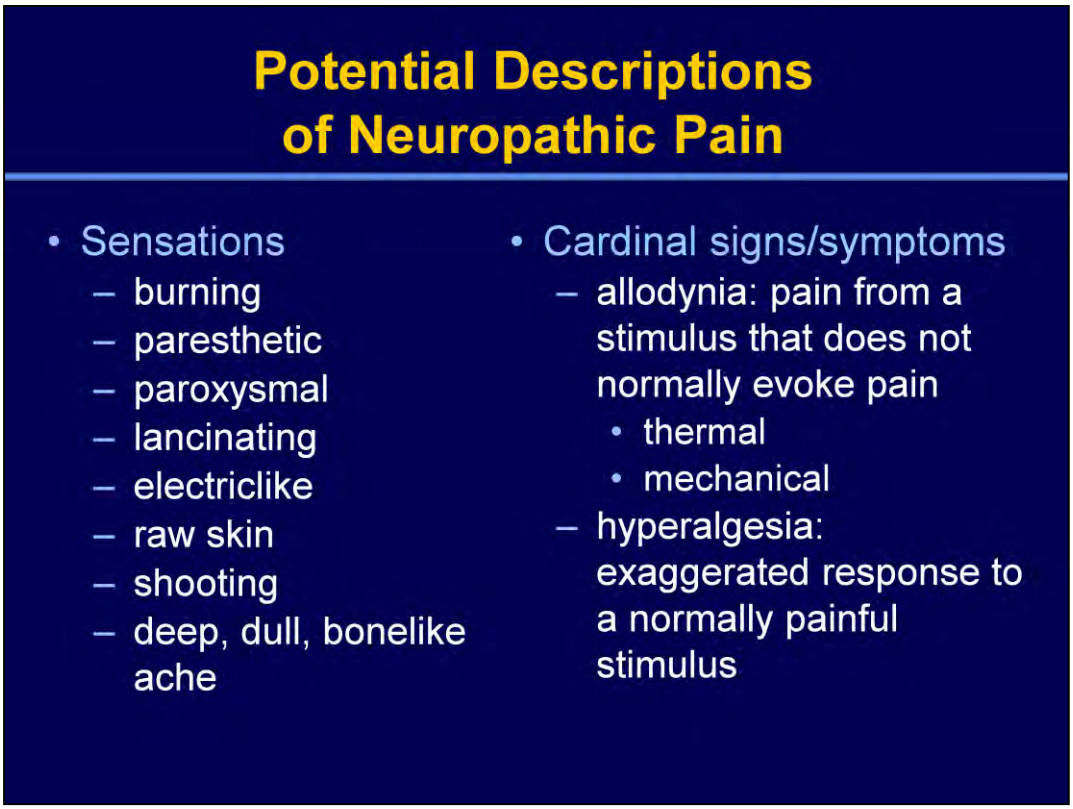
1. Galer BS, Dworkin RH. *A Clinical Guide to Neuropathic Pain*. Minneapolis, Minn: The McGraw-Hill Companies, Inc; 2000:15-19.
2. Eisendrath SJ. Psychiatric aspects of chronic pain. *Neurology*. 1995;45(suppl 9):S26-S34.



- Nociceptive, or inflammatory, pain is pain resulting from activity in neural pathways caused by potentially tissue-damaging stimuli.[1] Examples include postoperative pain, arthritis, mechanical low back pain, sickle cell crisis, and sports or exercise injuries.
- Neuropathic pain is pain caused by a primary lesion or dysfunction in the peripheral and/or central nervous systems.[2] Examples of peripheral neuropathic pain syndromes include human immunodeficiency virus (HIV) sensory neuropathy, postherpetic neuralgia (PHN), and diabetic neuropathy. Examples of central neuropathic pain include central poststroke pain, spinal cord injury pain, trigeminal neuralgia, and multiple sclerosis pain.
- As indicated by the “mixed type” area on the slide, chronic pain can be of mixed etiology with both nociceptive and neuropathic characteristics.
- Two types of neuropathic pain—PHN and diabetic neuropathy—will be emphasized within this module. These types of pain are being stressed because the great majority of randomized controlled trials of treatments for neuropathic pain have examined these two disorders, and because our understanding of the mechanisms of neuropathic pain is largely derived from those studies.

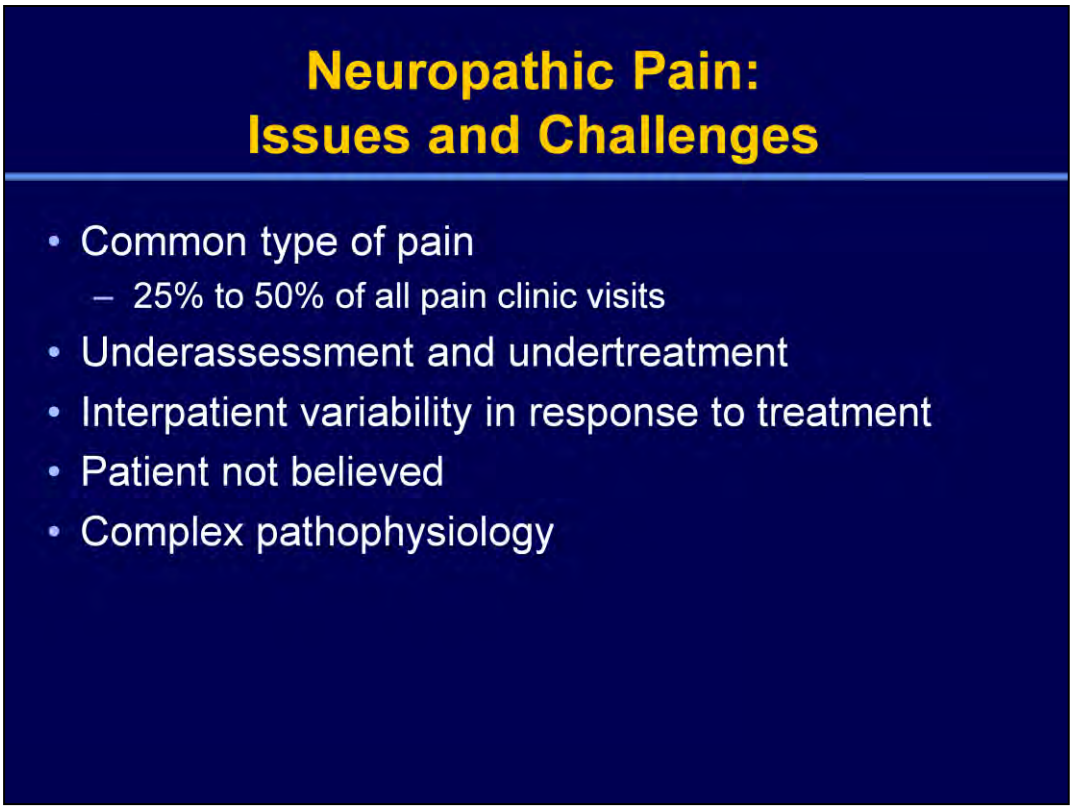
1. Portenoy RK, Kanner RM. Definition and Assessment of Pain. In: Portenoy RK, Kanner RM, eds. *Pain Management: Theory and Practice*. Philadelphia, Pa: FA Davis Company; 1996:4.
2. Galer BS, Dworkin RH. *A Clinical Guide to Neuropathic Pain*. Minneapolis, Minn: The

McGraw-Hill Companies Inc; 2000:8-9.



- A variety of terms are used to describe neuropathic pain, including those listed on the slide: burning, paroxysmal, paresthetic, lancinating, raw skin, shooting, electriclike, and deep, dull, and bonelike aching pain.
- Additional terms that are often used to describe neuropathic pain include squeezing, jabbing, broken-glass, cramping, spasms, icy cold, and frostbite.
- These terms are not perfectly sensitive or specific and are to be used only as a guide: some patients with neuropathic pain will not use these terms to describe their pain experience, and some patients who use these terms have nonneuropathic pain.
- Terms used to describe pain are usually not helpful in differentiating among neuropathic conditions.[1]
- The cardinal signs and symptoms of neuropathic pain are allodynia and hyperalgesia, both of which are defined on the slide.[2]

1. Galer BS. Neuropathic pain of peripheral origin: advances in pharmacologic treatment. *Neurology*. 1995;45(suppl 9):S17-S25.
2. Backonja M-M, Galer BS. Pain assessment and evaluation of patients who have neuropathic pain. *Neurol Clin*. 1998;16:775-789.



- Neuropathic pain is common and accounts for 25% to 50% of all visits to pain clinics.[1]
- Less than optimal education and training of physicians in pain disorders has led to the underassessment and undertreatment of patients. A survey of 313 practicing neurologists found that only 30% thought they had received sufficient training to diagnose pain diseases and only 20% felt they had enough training to treat pain adequately. Eighty-nine percent stated that more pain education is needed for resident training and 91% favored more pain training for practicing neurologists.[2] The American Board of Medical Specialties now offers board certification in pain medicine.
- The selection of therapy is difficult because neuropathic pain has a complex pathophysiology: the precise mechanisms are unknown and multiple mechanisms can coexist in individual patients.[3]
- Similarly, patients respond very differently to treatment. Physicians often need to resort to empirical treatment and sequential use of different pharmaceuticals and combinations of therapies.[4]

1. Davies HTO, Crombie IK, Macrae WA. Polarised views on treating neurogenic pain. *Pain*. 1993;54:341-346.
2. Galer BS, Keran C, Frisinger M. Pain medicine education among American neurologists: a need for improvement. *Neurology*. 1999;52:1710-1712.
3. Woolf CJ, Mannion RJ. Neuropathic pain: aetiology, symptoms, mechanisms, and management. *Lancet*. 1999;353:1959-1964.
4. Galer BS. Neuropathic pain of peripheral origin: advances in pharmacologic treatment. *Neurology*. 1995;45(suppl 9):S17-S25.

Human Models for Neuropathic Pain

- Diabetic neuropathy (DN) and postherpetic neuralgia (PHN) are the most prevalent neuropathic pain disorders
- Majority of randomized controlled trial data is on PHN/DN
- PHN has been the most commonly used model for treating neuropathic pain in clinical trials

- PHN is often used for investigating neuropathic pain because it is a readily distinguishable condition and manifests or persists after resolution of a herpes zoster rash, that is, after the initial injury has healed.[1]
- Additionally, the inefficacy of peripheral interventions in most PHN patients points to a predominating central pain generator, and thus implicates central nervous system (CNS) remodeling. Autopsy data confirm chronic peripheral inflammation, and also neuronal loss in dorsal root ganglia and reductions of both axons and myelin in affected nerves.[1]
- Although the actual CNS processes that result from the pathology and sustain the pain are not yet well understood, underlying mechanisms may include lowered threshold of activation or exaggerated activation, ectopic discharges, enlarged receptive fields, and collateral sprouting. These mechanisms are apparently common to other types of neuropathic pain.[2]
- Consequently, because PHN is such an inclusive human example of neuropathic pain, we will focus on that condition as we discuss the pathophysiology of neuropathic pain.

1. Portenoy RK. Neuropathic pain. In: Portenoy RK, Kanner RM, eds. *Pain Management: Theory and Practice*. Philadelphia, Pa: FA Davis Company; 1996:93-99.
2. Pappagallo M, Oaklander AL, Quatrano-Piacentini AL, et al. Heterogenous patterns of sensory dysfunction in postherpetic neuralgia suggest multiple pathophysiologic mechanisms. *Anesthesiology.* 2000;92:691-698

Estimated Prevalence of Neuropathic Pain in the United States*

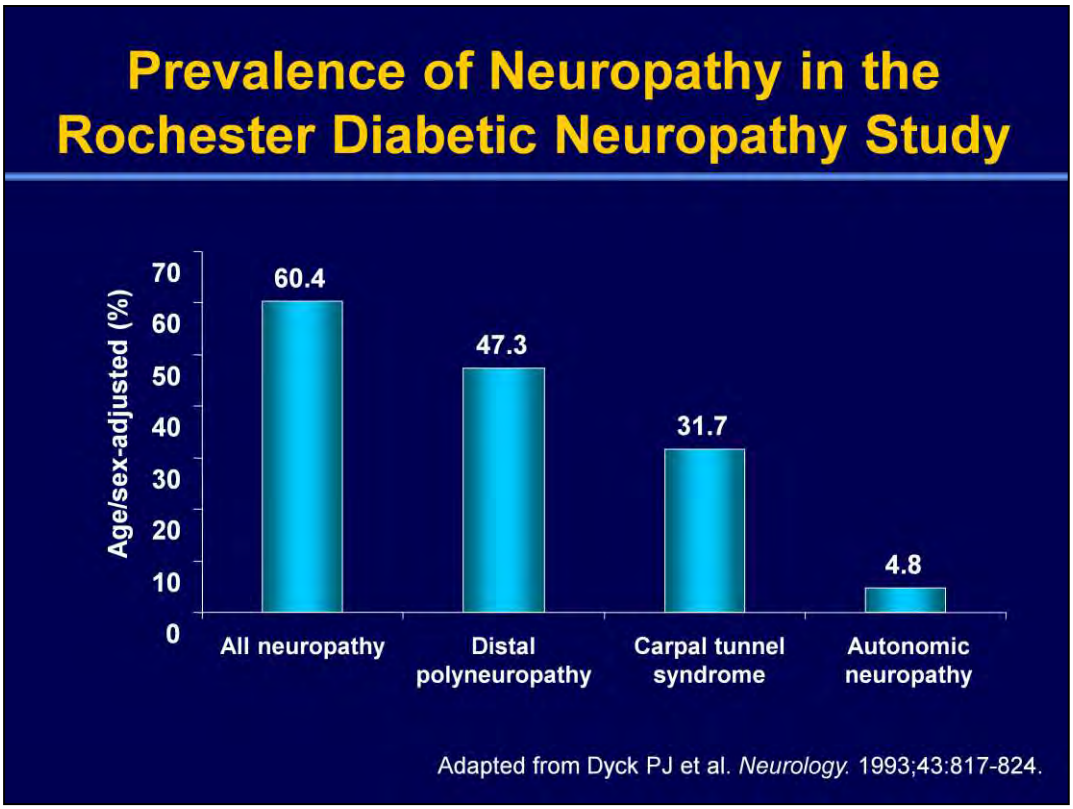
Condition	Number of Cases
Painful diabetic neuropathy	600,000
Postherpetic neuralgia (PHN)	500,000
Cancer-associated	200,000
Spinal cord injury	120,000
Causalgia and reflex sympathetic dystrophy (CRPS)	100,000
HIV-associated	100,000[1]
Multiple sclerosis	50,000
Phantom pain	50,000
Poststroke	30,000
Trigeminal neuralgia (tic douloureux)	15,000
Low back pain–associated	2,100,000
Total (excluding back pain)	**1,765,000**
Total (including back pain)	**3,865,000**

*Based on population of 270 million.

Adapted from Bennett GJ. *Hosp Pract*. 1998;33:95-114.
1. Schifitto G et al. *Neurology*. 2002;58:1764-1768.

- Very few careful studies have been conducted on the epidemiology of neuropathic pain, and the data presented in this slide are educated guesses about the prevalence of a number of neuropathic pain disorders.[1,3]
- If it is assumed that as few as 10% of patients with low back pain have pain that is primarily neuropathic in origin, then neuropathic low back pain is clearly the most prevalent neuropathic pain syndrome.[1]
- Prevalence estimates of neuropathic pain vary widely, depending on the results of clinical studies and the definition of pain. Differences may be explained in terms of pain tolerance: societies with a high toleration for pain will have fewer people with neuropathic and other types of chronic pain.[2]
- The terms causalgia and reflex sympathetic dystrophy (RSD) were reclassified as complex regional pain syndrome (CRPS) in the second edition of the IASP Classification of Chronic Pain Syndromes. CRPS type I was known as RSD and includes pain that does not involve obvious injury to the nervous system, whereas CRPS type II was known as causalgia and refers to pain with a nerve injury.

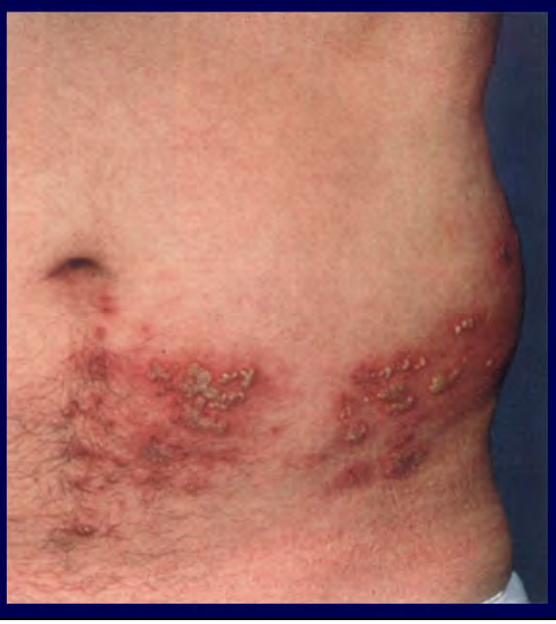
1. Bennett GJ. Neuropathic pain: new insights, new interventions. *Hosp Pract*. 1998;33:95-114.
2. Cunningham AL, Dworkin RH. The management of post-herpetic neuralgia. *BMJ*. 2000;321:778-779.
3. Schifitto G, McDermott MP, McArthur JC, et al. Incidence of and risk factors for HIV-associated distal sensory polyneuropathy. *Neurology*. 2002;58:1764-1768.



- Dyck et al undertook this study to address the lack of data about the health problems caused by diabetic neuropathies. The researchers invited all Rochester, Minnesota, residents with diabetes to respond to a cross-sectional and longitudinal study of diabetic neuropathies. A total of 380 people with insulin-dependent and noninsulin-dependent diabetes enrolled in the Rochester Diabetic Neuropathy Study.
- Results of the Rochester Diabetic Neuropathy Study indicate that the age- and sex-adjusted prevalence of all forms of neuropathy in patients with diabetes exceeds 60%.
- On an age- and sex-adjusted basis, nearly half of the patients in the study had distal polyneuropathy. Distal symmetric sensorimotor polyneuropathy is the most common form of neuropathy in patients with diabetes.
- Almost 5% of patients had autonomic neuropathy, or a neuropathy of the parasympathetic or sympathetic nerves of the autonomic nervous system.

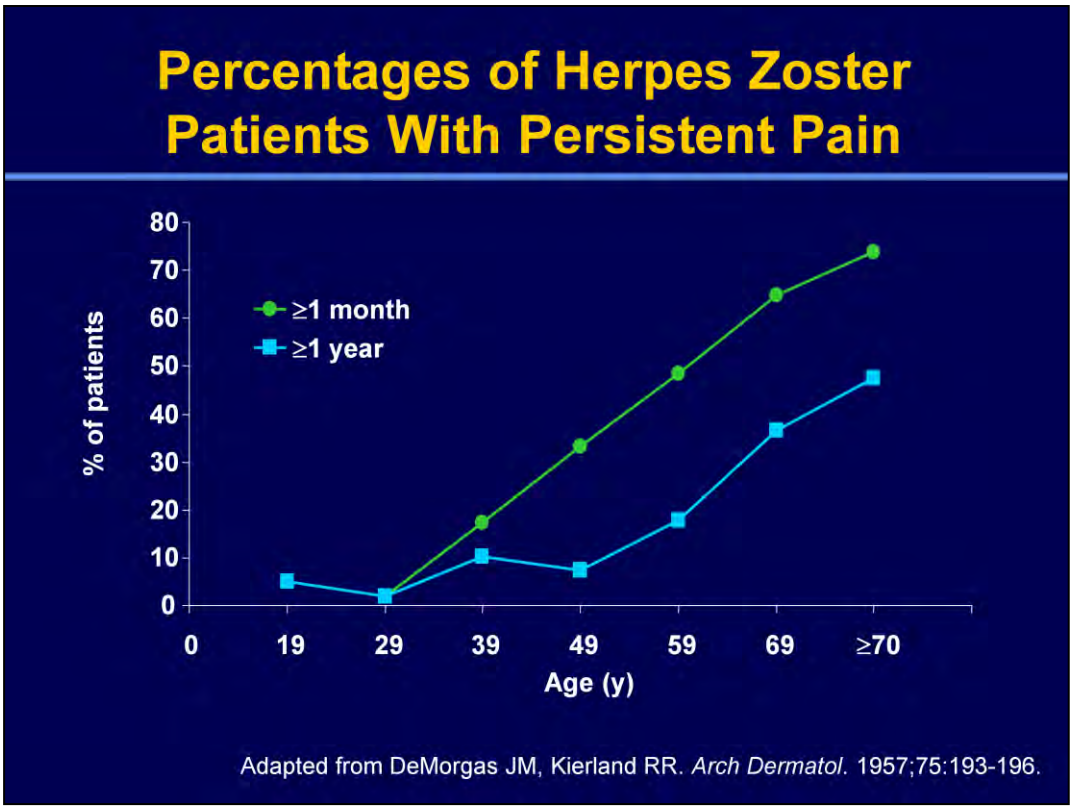
Dyck PJ, Kratz KM, Karnes JL, et al. The prevalence by staged severity of various types of diabetic neuropathy, retinopathy, and nephropathy in a population-based cohort: The Rochester Diabetic Neuropathy Study. *Neurology*. 1993;43:817-824.

Herpes Zoster (Thoracic Dermatome)



- The illustration above is of the grouped vesicles and erythema of a herpes zoster infection involving a left thoracic dermatome.
- Although any dermatome may be affected by herpes zoster, thoracic dermatomes are involved in at least 50% of acute zoster outbreaks and are the most commonly affected sites.[1]
- A distinctive characteristic of herpes zoster is the unilateral nature of the rash,[2] which does not cross the midline and is generally confined to the area of skin innervated by a single sensory ganglion (ie, a single dermatome).[3]
- Skin lesions typically resolve within 2 to 4 weeks after rash onset,[3] although persistent scarring and hypopigmentation in the affected area are common.[4]
- Many patients with herpes zoster experience a prodrome of unilateral pain or discomfort before the characteristic rash appears. This prodrome typically lasts only a few days before the rash appears, although prodromes with longer durations have been reported.[2]

1. Portenoy RK. Neuropathic pain. In: Portenoy RK, Kanner RM, eds. *Pain Management: Theory and Practice*. Philadelphia, Pa: FA Davis Company; 1996:99.
2. Eastern JS. Herpes zoster. *eMedicine Journal*. July 17, 2001. Available at: www.emedicine.com/DERM/topic180.htm. Accessed August 21, 2001.
3. Galer BS, Dworkin RH. *A Clinical Guide to Neuropathic Pain*. Minneapolis, Minn: The McGraw-Hill Companies, Inc; 2000:87-91.
4. An improving outlook for patients with postherpetic neuralgia. *Drug Ther Perspect*. 2001;17:8-11.



- These classic epidemiologic data show that the risk for persistent pain of 1 or more months' duration (upper line) or 1 or more years (lower line) increases with age in herpes zoster patients. One year after the onset of herpes zoster, only 4.2% of patients younger than 20 years were still experiencing pain, compared with 47% of patients older than 70 years.[1]
- Although, as shown on the graph, comparatively few patients younger than 40 years report pain 1 month after rash healing, almost 50% of herpes zoster patients older than 70 years continue to experience pain 1 year or more after the onset of their zoster infection.[2]
- Other risk factors associated with increased risk of PHN include greater severity of acute herpes zoster pain, greater herpes zoster rash severity/greater number of lesions, presence of a painful prodrome, and greater degree of sensory impairment in the affected dermatome.[2]
- Additional data suggest that the risk of PHN may be slightly increased in patients with ophthalmic zoster. Although the data are inconsistent, some reports suggest that women have a slightly higher incidence of PHN than do men.[3]

1. DeMorgas JM, Kierland RR. The outcome of patients with herpes zoster. *Arch Dermatol*. 1957;75:193-196.
2. Galer BS, Dworkin RH. *A Clinical Guide to Neuropathic Pain*. Minneapolis, Minn: The McGraw-Hill Companies, Inc; 2000:87-91.
3. Kost RG, Straus SE. Postherpetic neuralgia–pathogenesis, treatment, and prevention. *N Engl J Med*. 1996;335:32-42.

The Multidisciplinary Team

- Primary clinician
- Psychologist
- Neurologist
- Anesthesiologist
- Physical therapist
- Occupational therapist
- Psychiatrist
- Speech therapist
- Physician assistant
- Nurses (RN, NP)
- Neurosurgeon
- Social worker
- Pharmacist

- A number of studies suggest that success in pain management depends on a multidisciplinary approach that includes patient education, medications, physical therapy, and psychological counseling. For example, when Becker et al compared the effect of multidisciplinary pain treatment (MPT) with that of treatment by a general practitioner after initial supervision by a pain specialist (GP-group) on 189 patients with chronic, nonmalignant pain, they found that, after 6 months, the MPT group reported statistically significant reduction in pain intensity (VAS-score, $P<0.001$), improvement in psychological well-being (PGWB, $P<0.001$), quality of sleep ($P<0.05$), and physical functioning (SF-36-Physical Functioning, $P<0.05$) compared with the GP-group.
- A coordinated approach to pain management often provides the most efficient and cost-effective approach, which leads to patient empowerment (improved perception of personal control over pain) and the best clinical outcome.

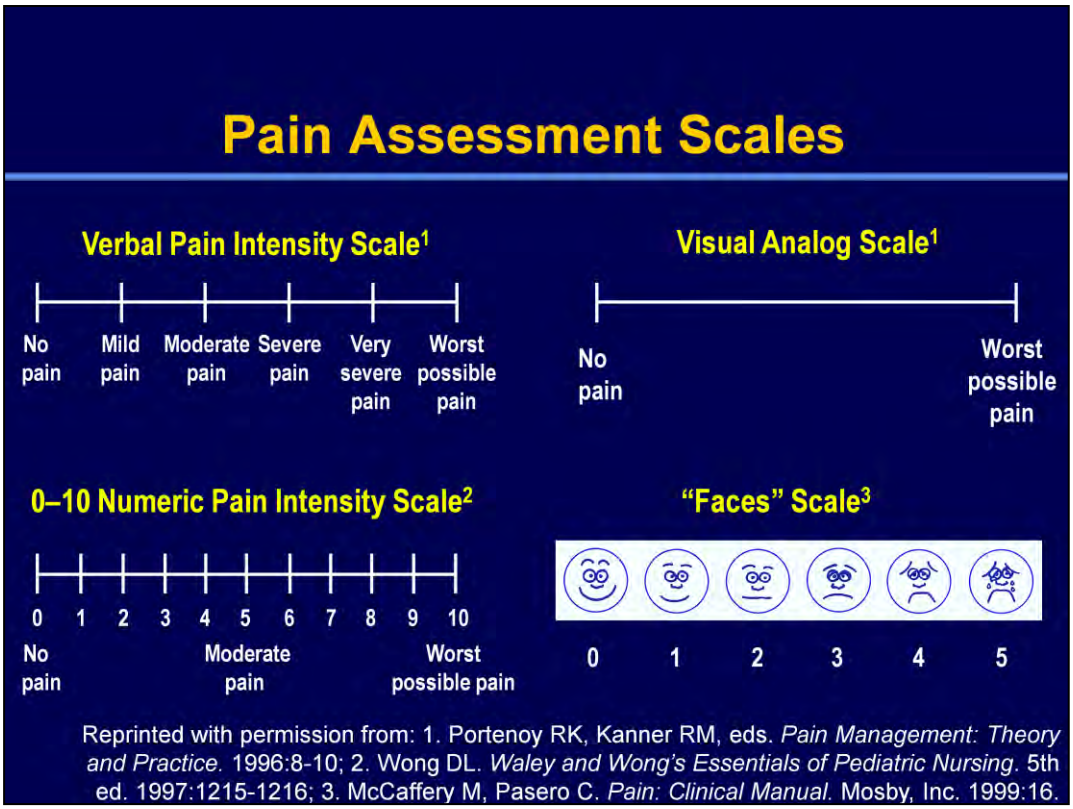
Becker N, Sjogren P, Bech P, Olsen AK, Eriksen J. Treatment outcome of chronic non-malignant pain patients managed in a Danish multidisciplinary pain centre compared to general practice: a randomized controlled trial. *Pain.* 2000;84:203-211.

Assessing the Patient Who Has Pain

- Onset and duration
- Location/distribution
- Quality
- Intensity
- Aggravating/relieving factors
- Associated features or secondary signs/symptoms
- Associated factors
  - mood/emotional distress
  - functional activities
- Treatment response

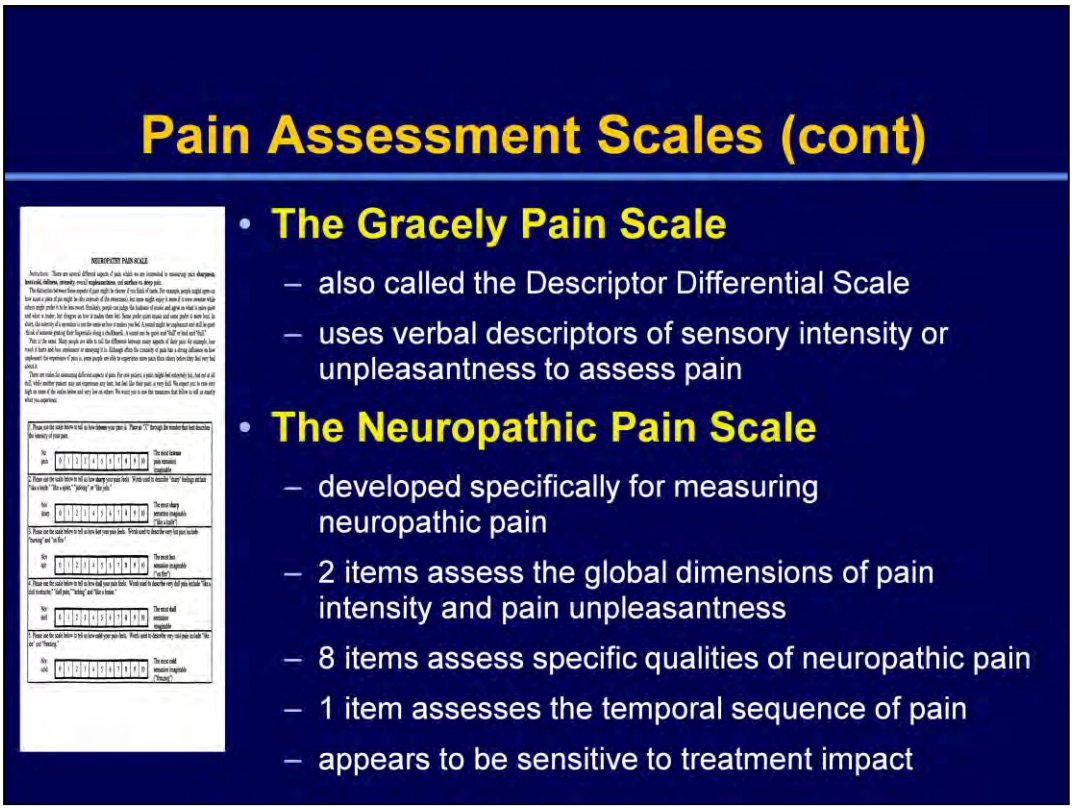
- Comprehensive pain assessment is now a regulatory (Joint Commission on Accreditation of Healthcare Organizations) mandate.
- Important characteristics of a patient's pain to be documented are listed above.[1,2]
- Assessment should include an evaluation of a patient's associated features and associated factors. The features include neurologic deficit and hyperphenomena, and among the associated factors are the psychosocial state (indicated by the patient's mood and level of emotional distress) and the impairment of functional activities, including activities of daily living, such as the ability to work or sleep.[1]
- Rational treatment cannot proceed without detailed records of previous treatments, including dosages, duration of therapy, side effects, and reason for stopping treatment.[1]

1. Backonja M-M, Galer BS. Pain assessment and evaluation of patients who have neuropathic pain. *Neurol Clin*. 1998;16:775-789.
2. Katz N. Neuropathic pain in cancer and AIDS. *Clin J Pain*. 2000;16(suppl 2):S41-S48.



- The slide depicts four of the pain scales that are used to assess a patient's pain. The scales are considered simple for patients to use as well as valid methods for measuring the severity of pain.[1-3]
- These scales can be used at the patient's bedside, and patients can be asked to respond to either a spoken or written question.
- With some scales, especially the visual analog scale, the patient marks the line at the point that best indicates the pain's intensity.
- The Wong-Baker FACES Pain Rating Scale is validated and recommended for patients aged 3 years and older. On this scale, Face 0 indicates no pain at all, Face 1 feels mild pain, Face 2 feels moderate pain, Face 3 feels severe pain, Face 4 feels very severe pain, and Face 5 feels the worst possible pain. The original appears above, and can be used as is or with the brief word descriptions under each number. In a study of 148 children aged 4 to 5 years, there were no differences in pain scores when children used the original or brief word instructions.[3]

1. Portenoy RK, Kanner RM. Definition and Assessment of Pain. In: Portenoy RK, Kanner RM, eds. *Pain Management: Theory and Practice*. Philadelphia, Pa: FA Davis Company; 1996:8-10.
2. McCaffery M, Pasero C. *Pain: Clinical Manual.* St. Louis, Mo: Mosby, Inc; 1999:16.
3. Wong DL. *Waley and Wong's Essentials of Pediatric Nursing*. 5th ed. St. Louis, Mo: Mosby, Inc; 1997:1215-1216.



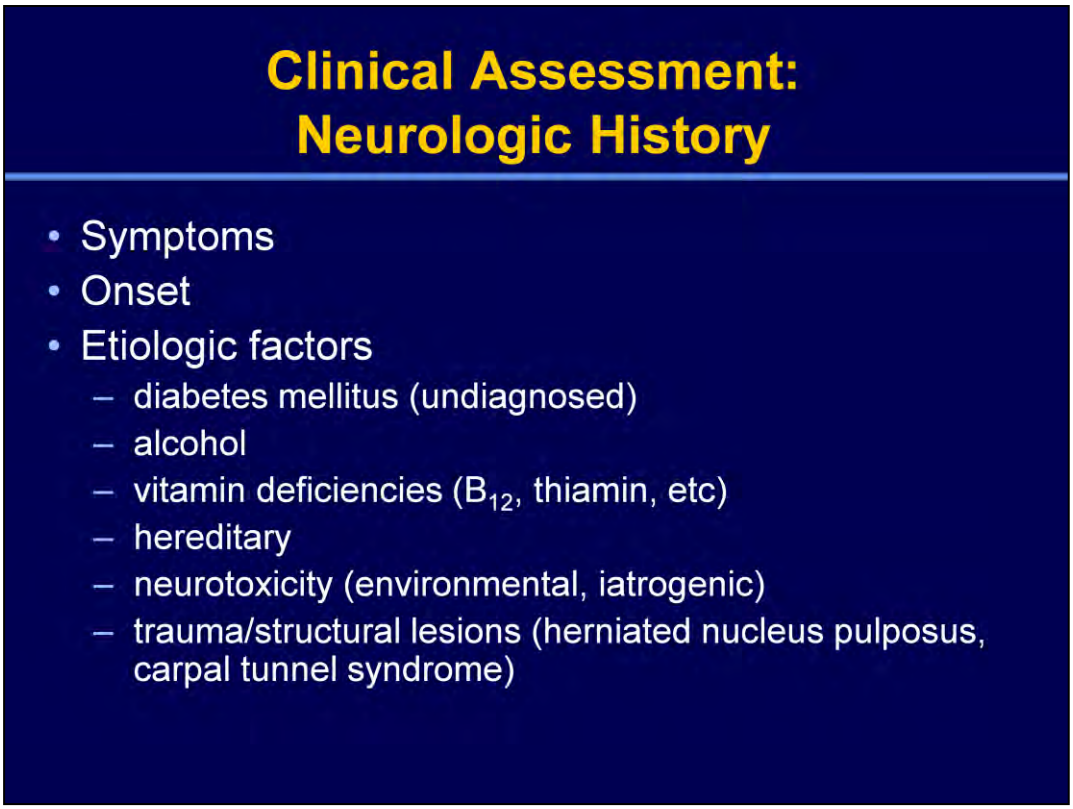
- Two other measurement instruments used to assess a patient's pain are the Gracely Pain Scale and the Neuropathic Pain Scale (NPS).
  - The Gracely Pain Scale, also called the Descriptor Differential Scale, uses quantified verbal descriptors of sensory intensity (ie, weak, mild, intense) or unpleasantness (ie, annoying, unpleasant, distressing) to assess the intensity or unpleasantness of sensations. The descriptors are assigned magnitudes on the basis of ratio-scaling procedures that demonstrated internal consistency, reliability, and objectivity. The scale has been shown to be a valid and reliable measurement of pain, especially in the clinical setting.[1]
  - The NPS was developed specifically for measuring neuropathic pain. It is designed to assess distinct pain qualities associated with neuropathic pain.[2]
    - The scale includes two items that assess the global dimensions of pain intensity and pain unpleasantness and includes eight items that assess eight specific qualities of neuropathic pain: "sharp," "hot," "dull," "cold," "sensitive," "itchy," "deep," and "surface." An eleventh item assesses the temporal sequence of pain.
    - Each of the 11 items is a 0 to 10 numerical score in which "0" is "no ___" and "10" is "the most ___ sensation imaginable."
  - NPS descriptors are, for the most part, statistically distinct from one another, and four of the items, "sharp," "sensitive," "cold," and "itchy" can distinguish PHN from other neuropathic pain syndromes. [2]
  - Moreover, the NPS items appear to be sensitive to the impact of treatments for neuropathic pain.[2]

1. Katz J, Melzack R. Measurement of pain. *Surg Clin North Am.* 1999;79:231-252.
2. Galer BS, Jensen MP. Development and preliminary validation of a pain measure specific

to neuropathic pain: the Neuropathic Pain Scale. *Neurology.* 1997;48:332-338.

Pain Assessment Scales (cont)

- **Brief Pain Inventory**: This easy-to-use tool was developed to specifically address the way in which increasing pain intensity will interfere with a person's quality of life and ability to function. It was originally developed to assess patients with cancer-related pain, but its use has now been generalized to many other painful states which are not cancer related.



- During the initial assessment, it is important to ascertain onset, associated symptoms, description, and temporal pattern of the pain (eg, intensity and frequency). Since pain may be secondary to disease, deficiency, environmental factors, and substance abuse, determining etiology is critical to selection of optimal therapy.

- Chronic pain, especially, may have a considerable psychosocial component. Patients with chronic pain report impairments of multiple QOL measures, including physical, social, and psychological well-being. Fifty-eight percent of patients with chronic pain have coexisting symptoms of depression or anxiety. Chronic, debilitating pain can significantly impact employment as well as severely stress the patient's marital and familial relationships.

Marcus DA. Treatment of nonmalignant chronic pain. *Am Fam Physician.* 2000;61:1331-1338,1345-1346.

Clinical Examination
General Physical Examination

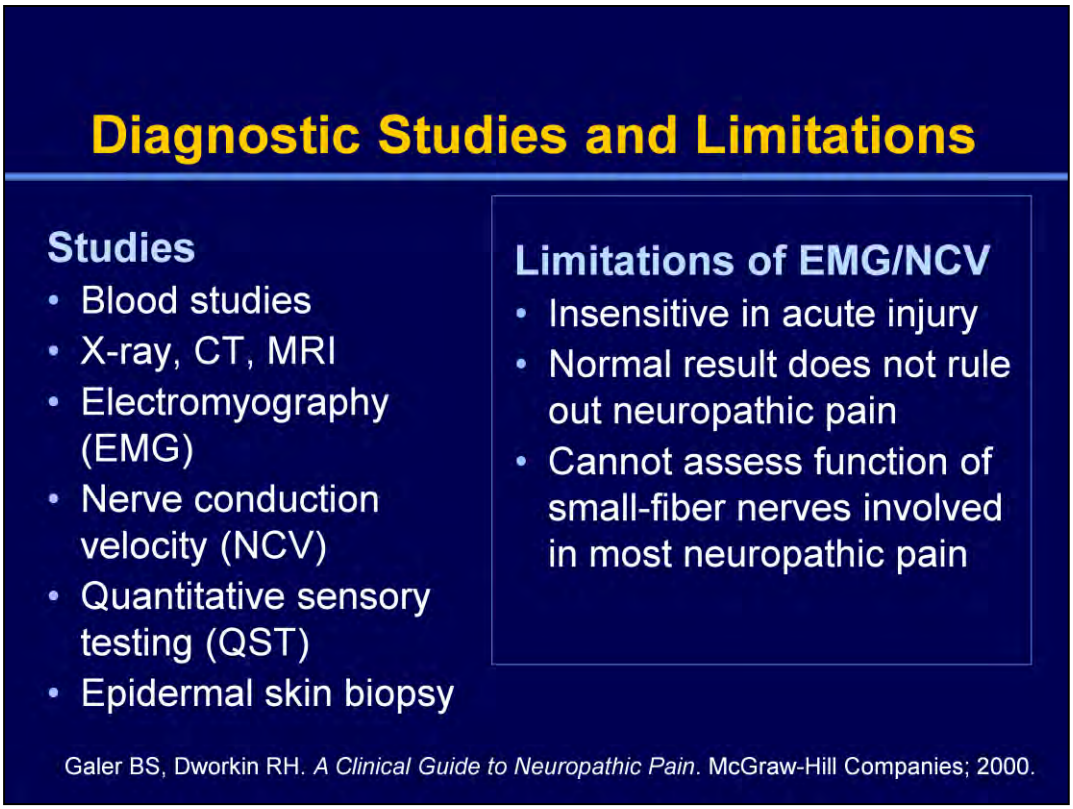
- General examination
- Musculoskeletal examination (muscles, joints, spine, ligaments)

Clinical Assessment: Definition of Terms

- **Mechanical allodynia**: abnormal perception of pain following a normally nonpainful stimulus
- **Thermal allodynia**: abnormal perception of pain from normally nonpainful cold or warm stimuli
- **Summation**: abnormal increase in pain perception with repeated stimuli, even as the stimulus remains constant in intensity

Clinical Assessment: Definition of Terms (cont)

- **After-sensation**: abnormal continued perception of a sensation after the stimulus has ceased
- **Hyperalgesia**: larger-than-expected pain response following a normally painful stimulus
- **Paresthesia/dysesthesia**: the perception of an abnormal sensation that is not painful (paresthesia) or which is painful (dysesthesia)



- Diagnostic studies can help confirm diagnostic impressions or rule out underlying causes (eg, rheumatologic causes) and diagnostic imperatives (eg, metastases in the cancer patient with new back pain).[1]
- Blood studies can help identify systemic illnesses (eg, acute herpes virus infection) associated with neuropathies.[1]
- Magnetic resonance imaging (MRI) can identify structural lesions, such as tumors or infections in the spine or plexus.[1,2]
- Computed tomography (CT) is similar to MRI, except it is less sensitive to soft tissue lesions.[1,2]
- Electromyography (EMG) and nerve conduction velocity (NCV) testing can help localize a neuropathy (eg, Is it a root or plexus neuropathy?), grade its severity, and help categorize the pathophysiology (axonal vs demyelinating).[1]
- Quantitative sensory testing (QST) assesses small-fiber function and can show abnormalities consistent with neuropathic pain even when EMG and NCV results are normal.[1]
- These studies have important limitations[1]:
  - They DO NOT MEASURE PAIN; a patient may have neuropathic pain and normal studies, or have abnormal studies with no pain.
  - EMG and NCV tests assess only large nerve fibers which have little involvement in pain.

1. Galer BS, Dworkin RH. *A Clinical Guide to Neuropathic Pain.* Minneapolis, Minn: McGraw-Hill Companies, Inc; 2000:50-51,93.
2. Foley KM. Pain syndromes in patients with cancer. In: Portenoy RK, Kanner RM, eds.

Pain Management: Theory and Practice. Philadelphia, Pa: FA Davis Company; 1996:194,199.

Neuropathic and Myofascial Pain

Allen G, Galer BS, Schwartz L. Epidemiology of complex regional pain syndrome: a retrospective chart review of 134 patients. *Pain.* 1999;80:539-544.

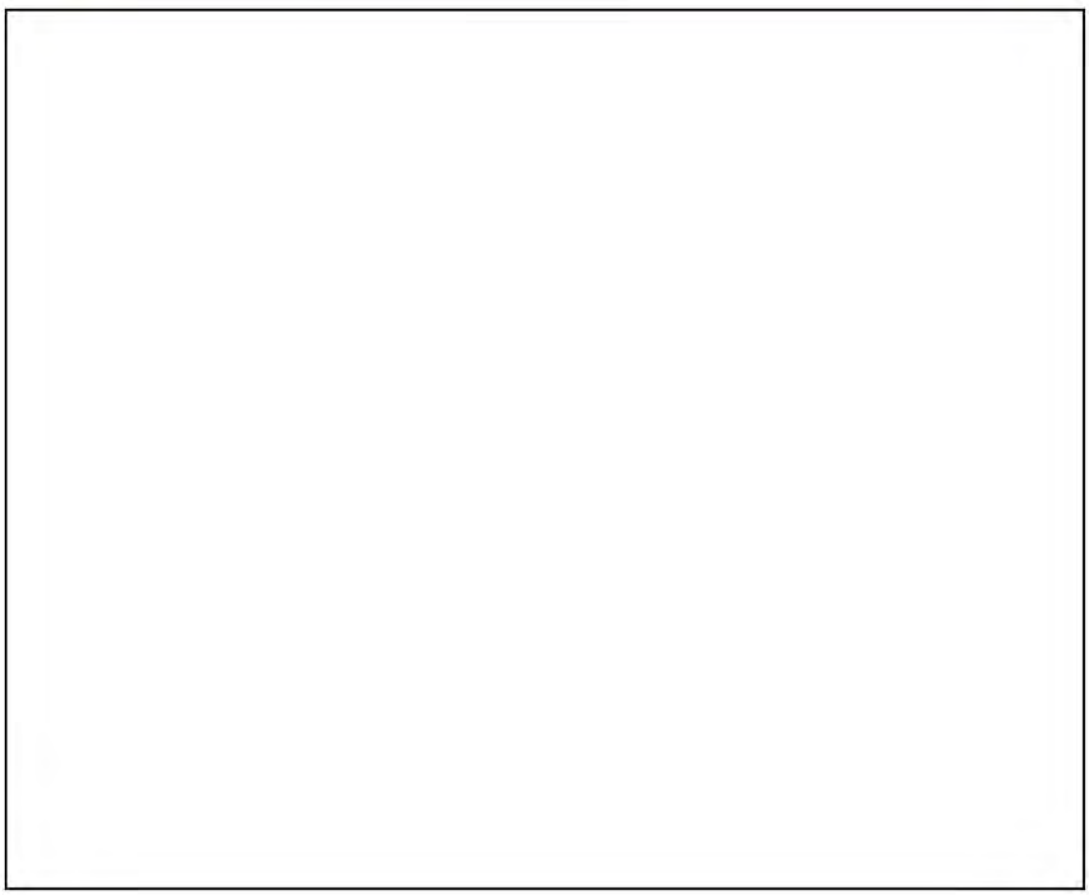
56% of patients had a myofascial component present at evaluation

Summary

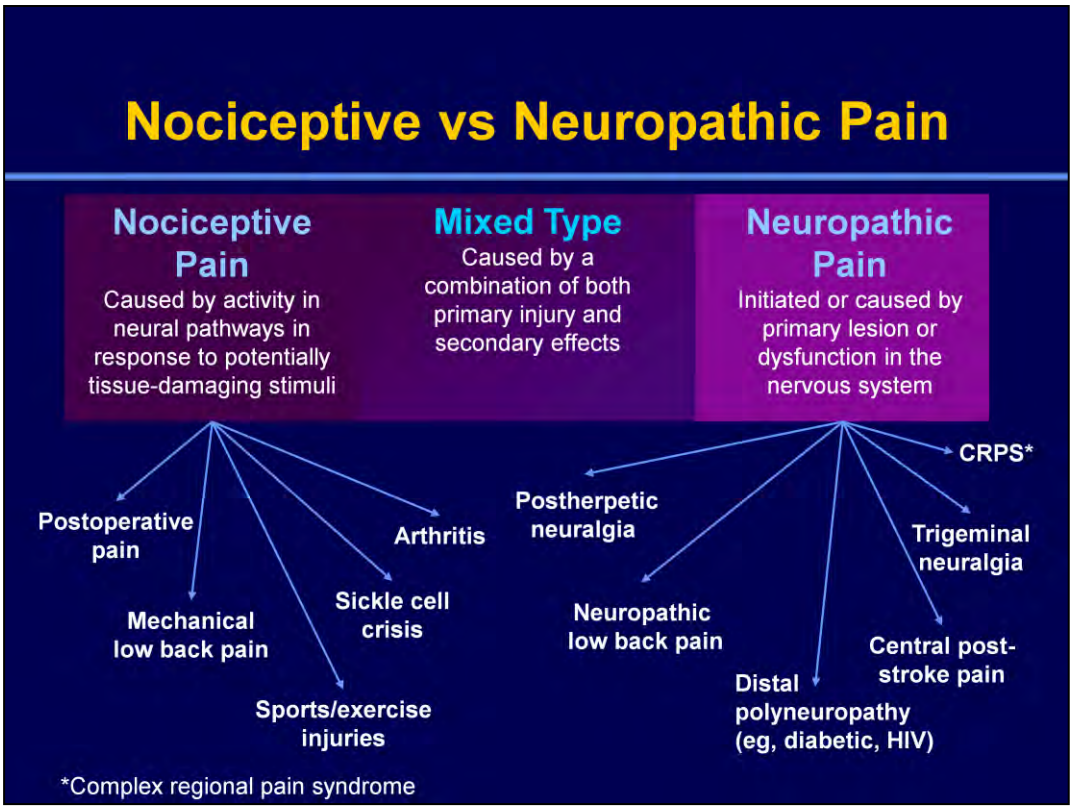
Based on findings noted from the history and physical examination, the diagnosis of neuropathic pain can be quite straightforward. Most often, a patient with neuropathic pain will also complain of other types of pain, eg, diabetic neuropathy and osteoarthritis; therefore, this must be addressed when treating the patient.

Case Study

- 64-year-old female with a past medical history of DM Type II and lumbar laminectomy (L4-5).
- Complains of low back, as well as lower extremity pain R>L.
- Additional complaints include numbness to both lower extremities, as well as hypersensitivity to any sensation involving her lower extremities.
- Physical examination demonstrates positive straight leg raising at 45 degrees pn to the right, hyperalgesia, and allodynia in the distal lower extremities to calf bilaterally.

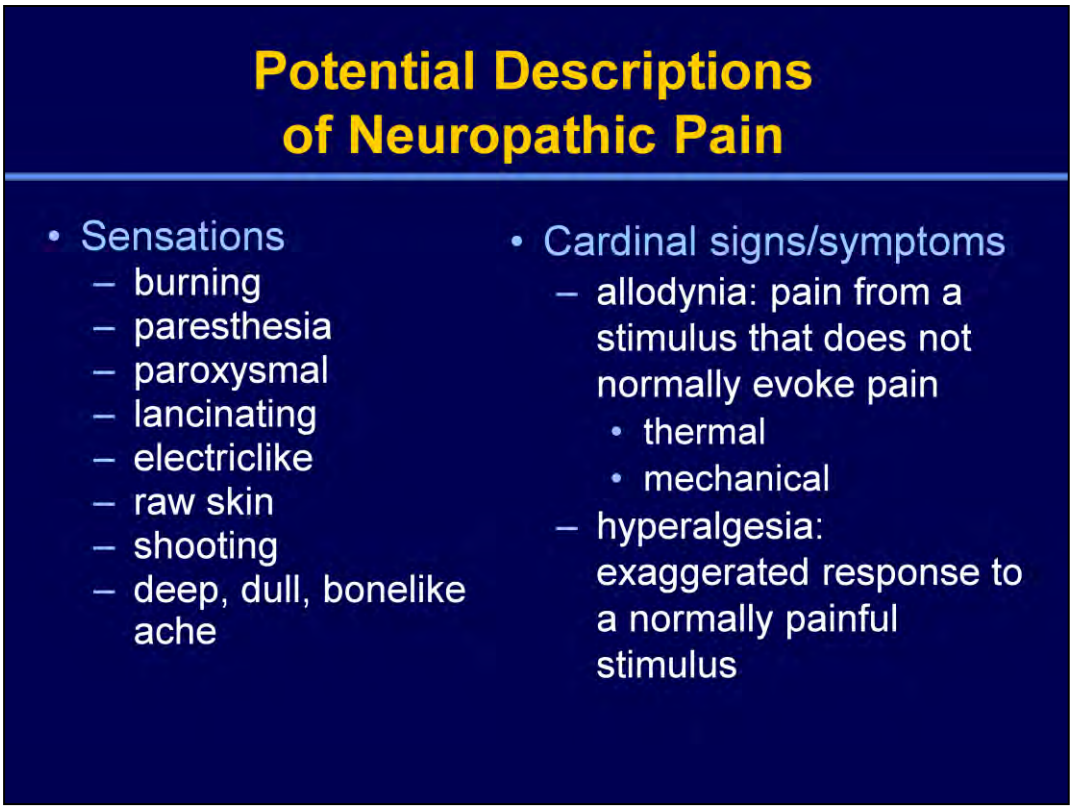



NATIONAL INITIATIVE ON PAIN CONTROL
THOMSON
PROFESSIONAL POSTGRADUATE SERVICES
Understanding the Underlying Mechanisms of Chronic Pain
Jianren Mao, MD, PhD
MGH Pain Center
Massachusetts General Hospital
Harvard Medical School
Boston, Massachusetts



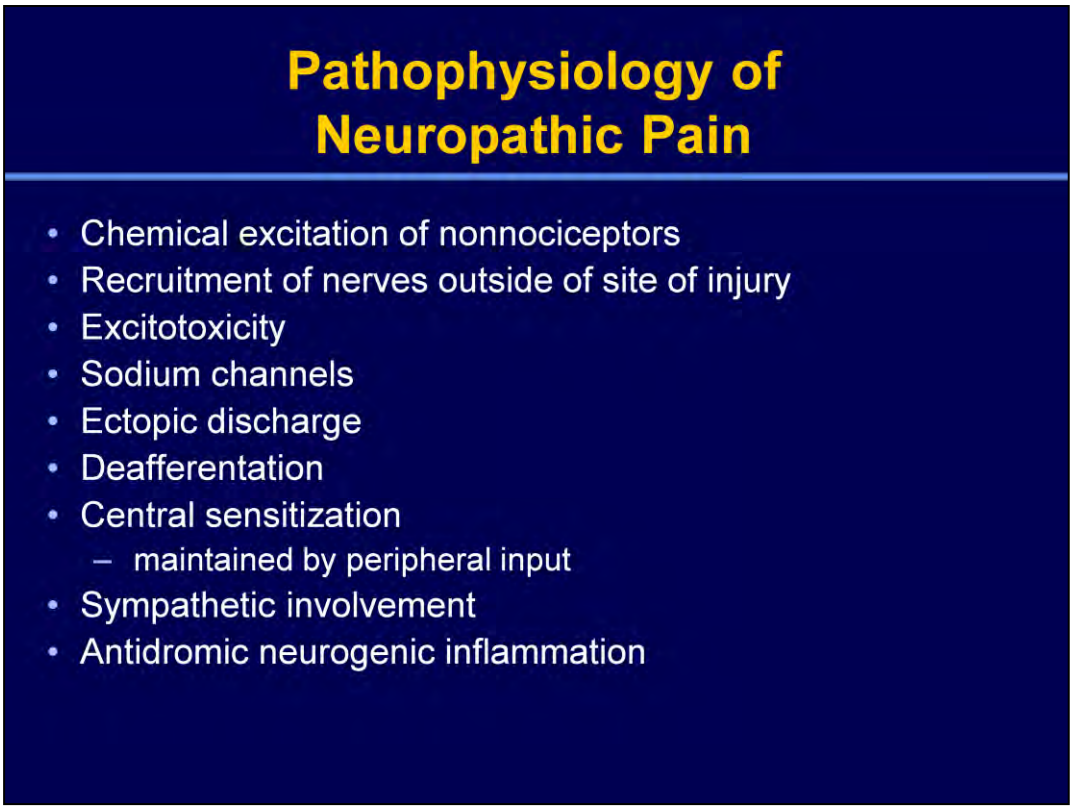
- Nociceptive, or inflammatory, pain is pain resulting from activity in neural pathways caused by potentially tissue-damaging stimuli.[1] Examples include postoperative pain, arthritis, mechanical low back pain, sickle cell crisis, and sports and exercise injuries.
- Neuropathic pain is pain caused by a primary lesion or dysfunction in the peripheral and/or central nervous systems.[2] Examples of peripheral neuropathic pain syndromes include HIV sensory neuropathy, postherpetic neuralgia (PHN), and diabetic neuropathy. Examples of central neuropathic pain include central poststroke pain, spinal cord injury pain, trigeminal neuralgia, and multiple sclerosis pain.
- As indicated by the “mixed type” area on the slide, chronic pain can be of mixed etiology with both nociceptive and neuropathic characteristics.
- Two types of neuropathic pain—PHN and diabetic neuropathy—will be emphasized within this module. These types of pain are being stressed because the great majority of randomized controlled trials of treatments for neuropathic pain have examined these two disorders, and because our understanding of the mechanisms of neuropathic pain is largely derived from those studies.

1. Portenoy RK, Kanner RM. Definition and Assessment of Pain. In: Portenoy RK, Kanner RM, eds. *Pain Management: Theory and Practice*. Philadelphia, Pa: FA Davis Company; 1996:4.
2. Galer BS, Dworkin RH. *A Clinical Guide to Neuropathic Pain*. Minneapolis, Minn: The McGraw-Hill Companies Inc; 2000:8-9.



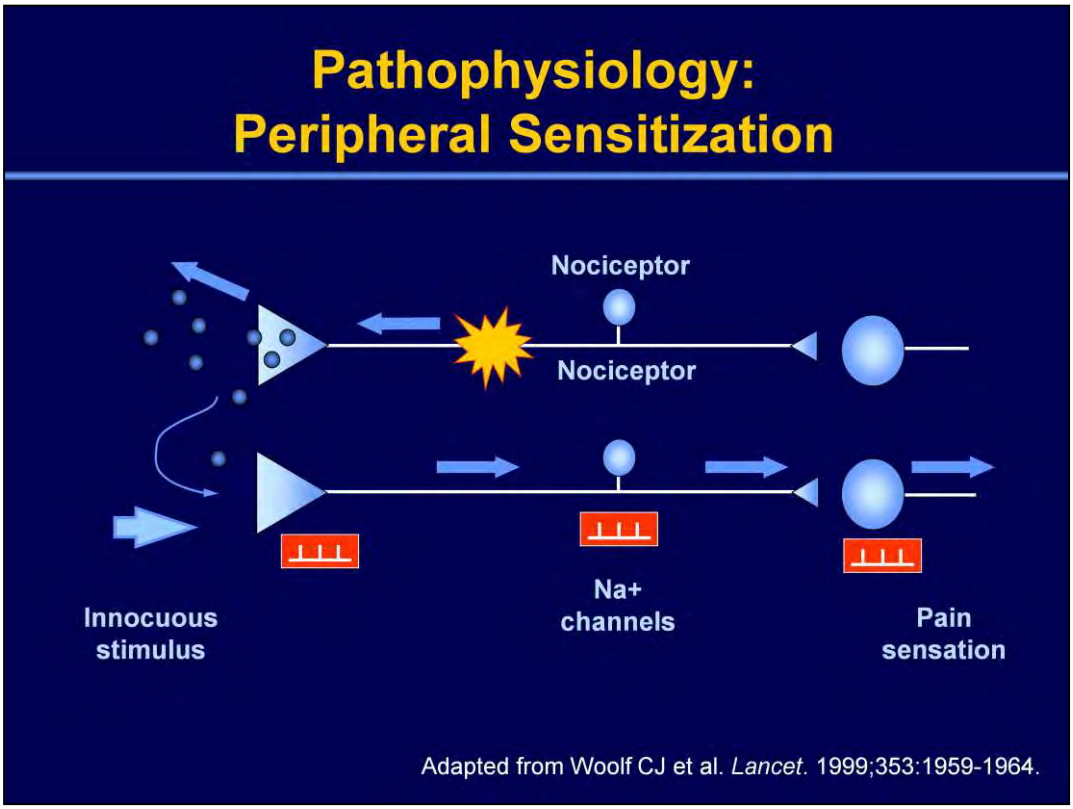
- A variety of terms are used to describe neuropathic pain, including those listed on the slide: burning, paroxysmal, paresthetic, lancinating, raw skin, shooting, electriclike, deep, dull, and bonelike aching pain.
- Additional terms that are often used to describe neuropathic pain include squeezing, jabbing, broken-glass, cramping, spasms, icy cold, and frostbite.
- These terms are not perfectly sensitive or specific and are to be used only as a guide: some patients with neuropathic pain will not use these terms to describe their pain experience, and some patients who use these terms have nonneuropathic pain.
- Terms used to describe pain are usually not helpful in differentiating among neuropathic conditions.[1]
- The cardinal signs and symptoms of neuropathic pain are allodynia and hyperalgesia, both of which are defined on the slide.[2]

1. Galer BS. Neuropathic pain of peripheral origin: advances in pharmacologic treatment. *Neurology*. 1995;45(suppl 9):S17-S25.
2. Backonja M-M, Galer BS. Pain assessment and evaluation of patients who have neuropathic pain. *Neurol Clin*. 1998;16:775-789.



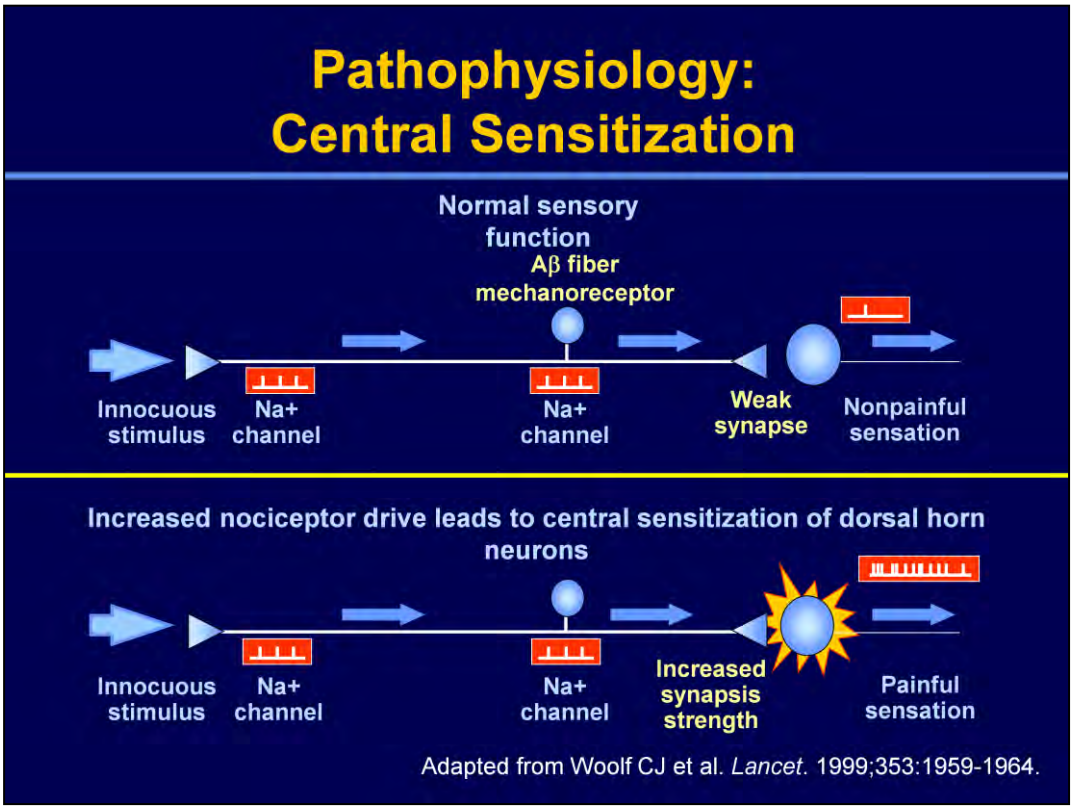
- Many mechanisms have been proposed for neuropathic pain, but it is unknown which mechanisms are most relevant in humans. This slide lists the more widely accepted proposed mechanisms. In an individual patient, more than one mechanism is probably relevant. The ability to classify patients based on predominant pathophysiology may, hopefully, help target therapy.[1]
- Excitotoxicity: nerve damage results in a barrage of nociceptive input released into the spinal cord that can damage inhibitory cells and result in a disinhibited pain system.[2]
- Sodium channels: in damaged nerves, abnormal sodium channels may be produced that result in hyperexcitable nerves.[3]
- Ectopic discharge: damaged nerves produce ectopic, or abnormal, nerve impulses that may promote pain perceptions.[3]
- Deafferentation: if the central nervous system (CNS) is deprived of normal nerve input, as in the case of amputation or plexus avulsion, pain may result. The classic picture is severe pain in an insensate (or absent) limb.[4]
- Central sensitization: with repeated sensory input, the CNS may become hyperresponsive (sensitized) to peripheral input, a so-called facilitated state. This state is caused by long-term or permanent changes in the anatomy or physiology of the CNS produced by pain.[1-3]

1. Galer BS. Neuropathic pain of peripheral origin: advances in pharmacologic treatment. *Neurology*. 1995;45(suppl 9):S17-S25.
2. Brookoff D. Chronic pain: 1. A new disease? *Hosp Pract*. July, 2000:45-59.
3. Baron R. Peripheral neuropathic pain: from mechanisms to symptoms. *Clin J Pain*. 2000;16:S12-S20.
4. Portenoy RK. Neuropathic pain. In: Portenoy RK, Kanner RM, eds: *Pain Management*: *Theory and Practice*. Philadelphia, Pa: FA Davis Company; 1996:94,97.



- The upper figure illustrates how damage to a peripheral nerve (the starburst) causes "algesic substances" to be released from the peripheral nerve terminal. The algesic substances may induce action potentials in the surrounding, intact neurons.
- Nerve injury may mediate dedifferentation of Schwann cells, causing the loss of the axon-insulation and myelin-production capabilities of these cells.
- The lower figure shows how, after this damage, the nerve may become hyperresponsive to noxious or nonnoxious stimulation, facilitating pain.

Woolf CJ, Mannion RJ. Neuropathic pain: aetiology, symptoms, mechanisms, and management. *Lancet*. 1999;353:1959-1964.



- The upper portion of the slide illustrates the normal function of an Aβ nerve fiber and its dorsal horn connection. An innocuous brush-evoked stimulus activates the fiber's mechanoreceptor, but the stimulus is not adequate to activate the dorsal horn pain pathway across a weak synapse.
- The lower portion of the slide illustrates central sensitization, by increased nociceptor drive, of the dorsal horn neuron (represented by the starburst). The Aβ fiber input is now sufficient to activate spinal cord pain pathways.
- Central sensitization may result from:
  - An effective increase in the area of the periphery eligible to activate neurons
  - An exaggerated response to a stimulus that meets the activation threshold
  - A stimulus that had been too weak to satisfy the activation threshold becomes an irritating stimulus

Woolf CJ, Mannion RJ. Neuropathic pain: aetiology, symptoms, mechanisms, and management. *Lancet*. 1999;353:1959-1964.

Proposed Postherpetic Neuralgia Subtypes

	Irritable Nociceptor	Deafferentation With Allodynia	Deafferentation Without Allodynia
Thermal sensory deficit	+/-	+++	+++
Allodynia	+++	+++	None
Local anesthetic skin infiltration	Marked relief	Absent or minimal	Absent or minimal
Mechanism	Functionally abnormal nociceptors and central sensitization	Deafferentation with abnormal central connections	Deafferentation with central hyperactivity

Adapted from Fields HL et al. *Neurobiol Dis*. 1998;5:209-227.

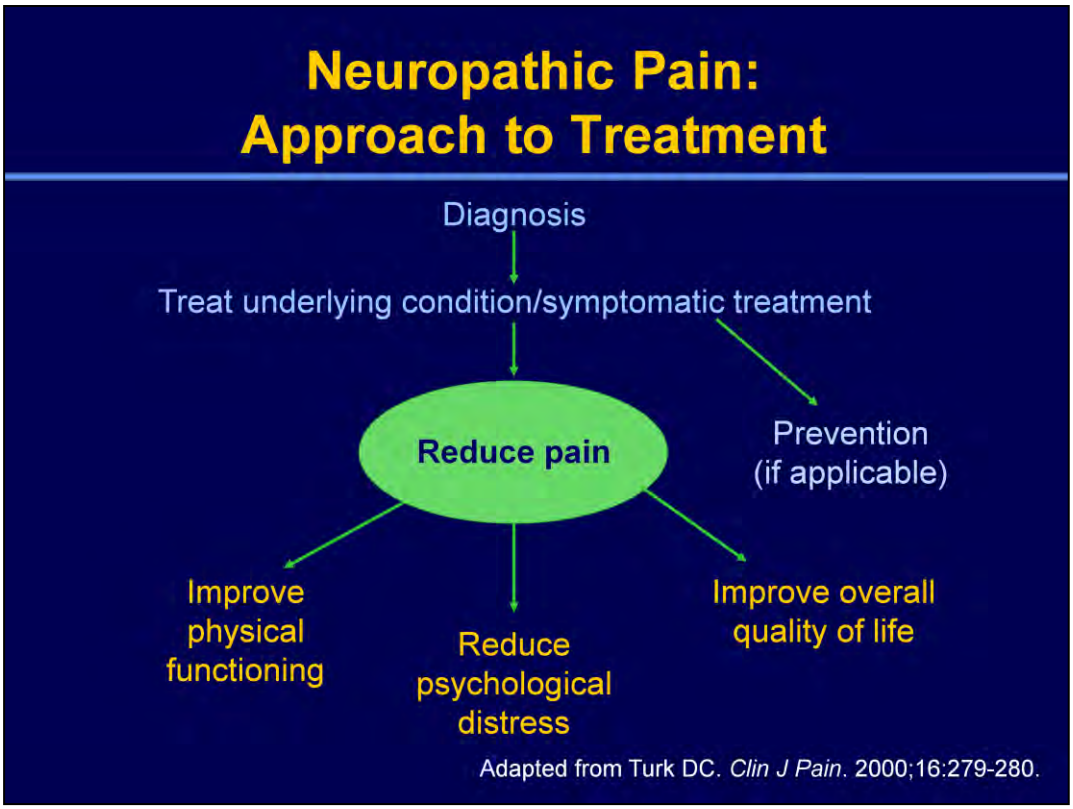
- Using clinical and experimental data, Fields and Rowbotham have proposed that three subtypes of PHN may coexist in individual patients: an irritable nociceptor type and two deafferentation types (one with and one without allodynia caused by a light, moving mechanical stimulus)[1]:
  - Irritable nociceptor subtype. These patients characteristically have functionally abnormal, yet anatomically intact, primary afferents that generate pain and maintain allodynia via central sensitization. These patients usually have minimal sensory loss and are responsive to anesthetic skin infiltration.[2]
  - Deafferentation subtype with allodynia. These patients have pain associated with small-fiber deafferentation. Pain and temperature sensation are profoundly impaired and marked dynamic mechanical allodynia exists. This allodynia is proposed to result from abnormal central connections between large-diameter peripheral afferents and central pain transmission neurons. Local skin infiltration with an anesthetic agent produces no change.[2]
  - Deafferentation subtype without allodynia. These patients experience constant pain without significant allodynia in an area of profound sensory loss. In these patients, deafferentation is thought to initiate change in the activation state of central pain transmission neurons. Local anesthetic infiltration does not affect continuing pain.[2]
- Distinguishing among the subtypes might be a rational method to help determine appropriate therapy.

1. Rowbotham MC, Petersen KL, Fields HL. Postherpetic neuralgia more than one disorder? *Pain Forum*. 1998;74:231-237.
2. Fields HL, Rowbotham M, Baron R. Postherpetic neuralgia: irritable nociceptors and deafferentation. *Neurobiol Dis*. 1998;5:209-227.

Treatment of Neuropathic Pain

"Undertreatment of acute and chronic pain persists despite decades of efforts to provide clinicians with information about analgesics."

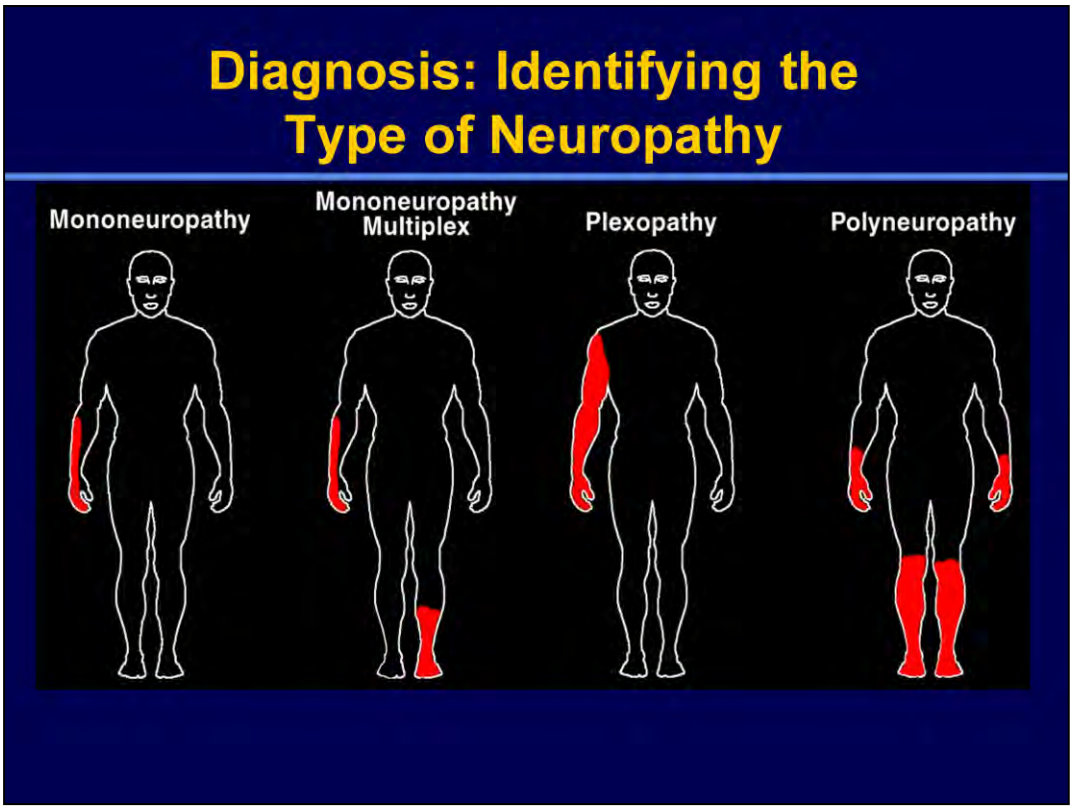
American Pain Society Quality of Care Committee. Quality improvement guidelines for the treatment of acute pain and cancer pain. *JAMA*. 1995;274:1874-1880.



- The management of neuropathic pain encompasses establishing a diagnosis, treating any underlying condition that may be causing the pain, providing symptomatic relief from pain and disability, and preventing recurrence.
- Neuropathic pain is often diagnosable as a specific entity, for example, as peripheral neuropathy or malignant radiculopathy.[1,2]
- Depending on the underlying condition, patients could receive relief from pain through surgical release of an entrapped nerve,[2] epidural steroids for lumbar radiculopathy,[3] or antivirals for herpes zoster.[4]
- Symptomatic treatment should be offered when specific treatment is not available or is ineffective in reducing pain; measures to reduce disability should be advised.[4]
- Treatment for patients with long-standing neuropathic pain rarely eliminates the pain. Consequently, treatment of chronic pain should have the following clinically meaningful goals, which can be achieved in a considerable proportion of patients who experience chronic pain:
  - Reducing pain
  - Improving physical functioning
  - Reducing psychological distress
  - Improving overall quality of life (QOL)
- It is important for both physicians and patients to have appropriate expectations for the outcome of treatment. For example, patients should be aware at the start of treatment that it is unlikely that their pain will be completely eliminated but that treatment can improve their QOL.[5]
- In some instances, preventive measures are available; for example, maintaining tight glycemic control for patients with diabetic neuropathy,[2] or providing antiviral agents for patients with acute herpes zoster to prevent postherpetic neuralgia (PHN).[4] Patients

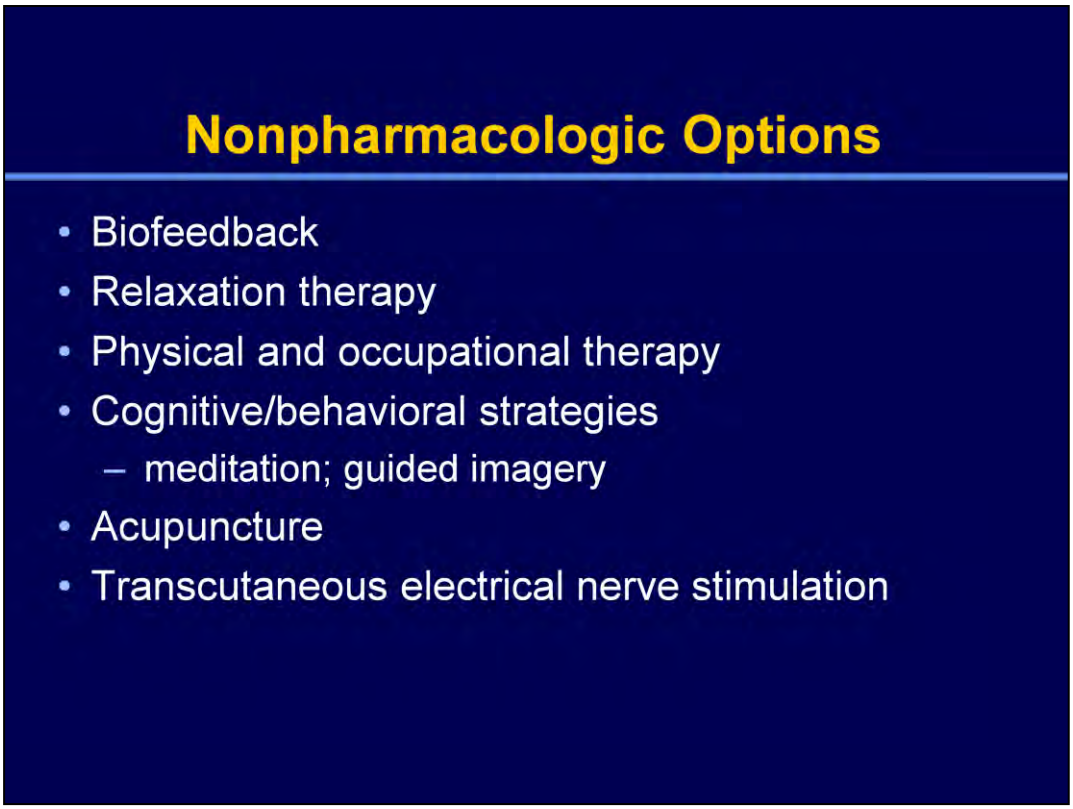
who are at risk for chronic pain should receive preventative treatment.

1. Katz N. *Clin J Pain*. 2000;16:S41-S48; 2. Belgrade MJ. *Postgrad Med*. 1999;106:127-148;
3. Kim KM, Kim HS, Choi KH, Ahn WS. *J Korean Med Sci*. 2001;16:193-197; 4.Galer BS, Dworkin RH. *A Clinical Guide to Neuropathic Pain*. Minneapolis, Minn: McGraw-Hill Companies Inc; 2000:11,90; 5.Turk DC. *Clin J Pain*. 2000;16:279-280.



- The first priority in treating neuropathic pain is to establish a diagnosis. This not only assists in determining a treatment plan, but also helps the patient understand the nature of his or her chronic pain.
- Diagnosis of neuropathic pain requires identifying the nerve structures that are involved. Pattern recognition is a common means of identifying the location of the deficit. Once the pattern of involvement is recognized, the next step is to identify the etiology.
- Mononeuropathies are usually posttraumatic or caused by entrapment neuropathies.[1] Occasionally systemic disease (eg, diabetes, vasculitis) can produce a mononeuropathy.[2]
- Mononeuropathy multiplex means that a patient has multiple mononeuropathies, usually asymmetric and involving multiple parts of the body. Causes include vasculitis, sarcoidosis, and inflammatory polyneuropathies.[2]
- Plexopathies involve most of an extremity, often originating at the plexus.[2,3] Common causes include trauma, cancer, radiation, and some systemic illnesses.[3]
- Peripheral polyneuropathy, resulting in a “stocking-and-glove” pattern, is perhaps the pattern most easily recognized.[4] It is always the result of a systemic process, such as a toxic exposure, diabetes, or alcohol.[1]

1. Boulton AJM, Malik RA. Diabetic neuropathy. *Med Clin North Am*. 1998;82:909-929.
2. Portenoy RK. Neuropathic Pain. In: Portenoy RK, Kanner RM, eds. *Pain Management: Theory and Practice*. Philadelphia, Pa: FA Davis Company; 1996:108-113.
3. Katz N. Neuropathic pain in cancer and AIDS. *Clin J Pain*. 2000;16:S41-S48.
4. Galer BS, Dworkin RH. *A Clinical Guide to Neuropathic Pain*. Minneapolis, Minn: McGraw-Hill Companies Inc; 2000:100.



- Nonpharmacologic strategies may be useful in easing pain and improving function, especially if used adjunctively with pharmacologic remedies. However, nonpharmacologic strategies are rarely sufficient to replace pharmacotherapies, especially in the case of chronic neuropathic pain.[1]
- A number of trials have demonstrated that transcutaneous electrical nerve stimulation has efficacy in ameliorating chronic neuropathic pain. However, the apparatus may be difficult for some patients to operate and the treatment itself is time-consuming.[2]

1. Ferrell B, Herr K, Epplin J, et al. The management of persistent pain in older persons. *Programs and Abstracts of the American Geriatric Society 2002 Annual Scientific Meeting*. May 8–12, 2002; Washington, DC.
2. Kuman D, Marshall HJ. Diabetic peripheral neuropathy: amelioration of pain with transcutaneous electrostimulation. *Diabetes Care*. 1997;20:1702-1705.


How Do Patients Choose?
Excedrin
Advil
IBUPROFEN
Excedrin IB
Aspirin Free
Excedrin
Excedrin
Advil
NUPRIN
IBUPROFEN
TYLENOL
Tablets
REGULAR STRENGTH
TYLENOL
Tablets
TYLENOL
Extended Relief
TYLENOL
Extended Relief
REGULAR STRENGTH
PAIN RELIEVER
REGULAR STRENGTH
PAIN RELIEVER
REGULAR STRENGTH
PAIN RELIEVER
Motrin
IB
Motrin
IB
Motrin
IB
BAYER
BAYER
BAYER
Ecotrin
Ecotrin
Ecotrin
Ecotrin


Aim for Monotherapy
Titrate only one drug at a time

Pharmacotherapy Guidelines

1. Medication must result in:
   - significant pain relief
   - tolerable side effects

⟹ ↑ function

Pharmacotherapy Guidelines (cont)

2. Both physician and patient must realize significant individual variability

Pharmacotherapy Guidelines (cont)

3. Slow titration until:
   a) significant pain relief
   b) intolerable side effects
   c) "toxic serum level"

Pharmacotherapy Guidelines (cont)

4. Educate the patient

Pharmacotherapeutic Considerations: Setting Priorities

- Efficacy
  - clinical trial data
  - clinical experience
- Safety/tolerability
- Ease of use
  - dosing
  - titration
  - drug-drug interactions
  - patient acceptability
- Cost

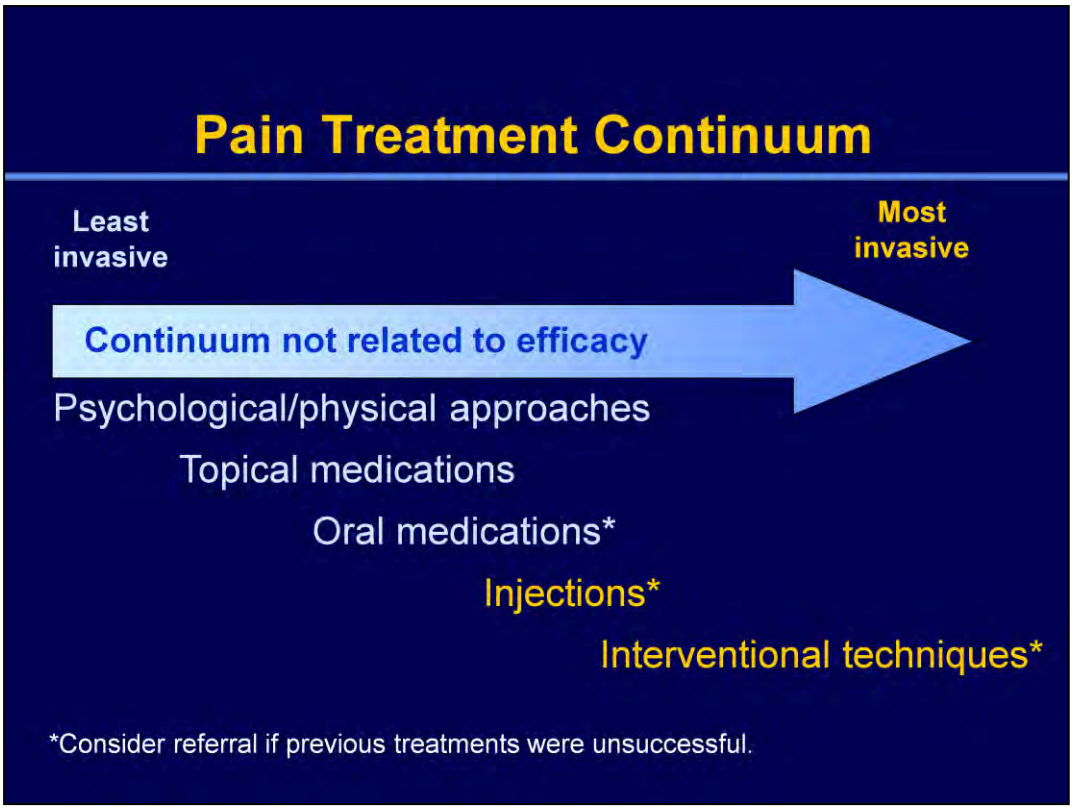
- Since nonpharmacologic treatment is often not sufficient for patients with neuropathic pain, pharmacotherapy constitutes the primary clinical approach.
- How does one decide which treatment to offer?
  - First, determine there is evidence that the treatment works: the better the evidence, the more motivated physicians are to use that treatment. The hierarchy of strength of evidence, such as clinical trials or case series, should be considered.[1,2]
  - Safer treatments are used first.[1]
  - Convenience of administration is important because it enhances QOL, facilitates compliance, and leads to efficacy.[3]
- In this era of managed care with pharmaceutical formularies, the cost of a medication frequently has bearing on how often it will be used.

1. Sindrup SH, Jensen TS. Efficacy of pharmacological treatments of neuropathic pain: an update and effect related to mechanism of drug action. *Pain.* 1999;83:389-400.
2. Galer BS. Neuropathic pain of peripheral origin: advances in pharmacologic treatment. *Neurology*. 1995;45(suppl 9)S17-S25.
3. Nies AS, Spielberg SP. Principles of therapeutics. In: Hardman JG, Gilman AG, Limbird LE, eds. *Goodman and Gilman's The Pharmacological Basis of Therapeutics*. 9th ed. New York, NY: McGraw-Hill Companies Inc; 1996:51-52, 1704-1705.

Pharmacotherapy

- Topical agents
- Anticonvulsants
- Antidepressants
- Opiates
- Oral local anesthetics
- α-Adrenergic agents
- Neuroleptics
- NMDA-receptor antagonists
- Others

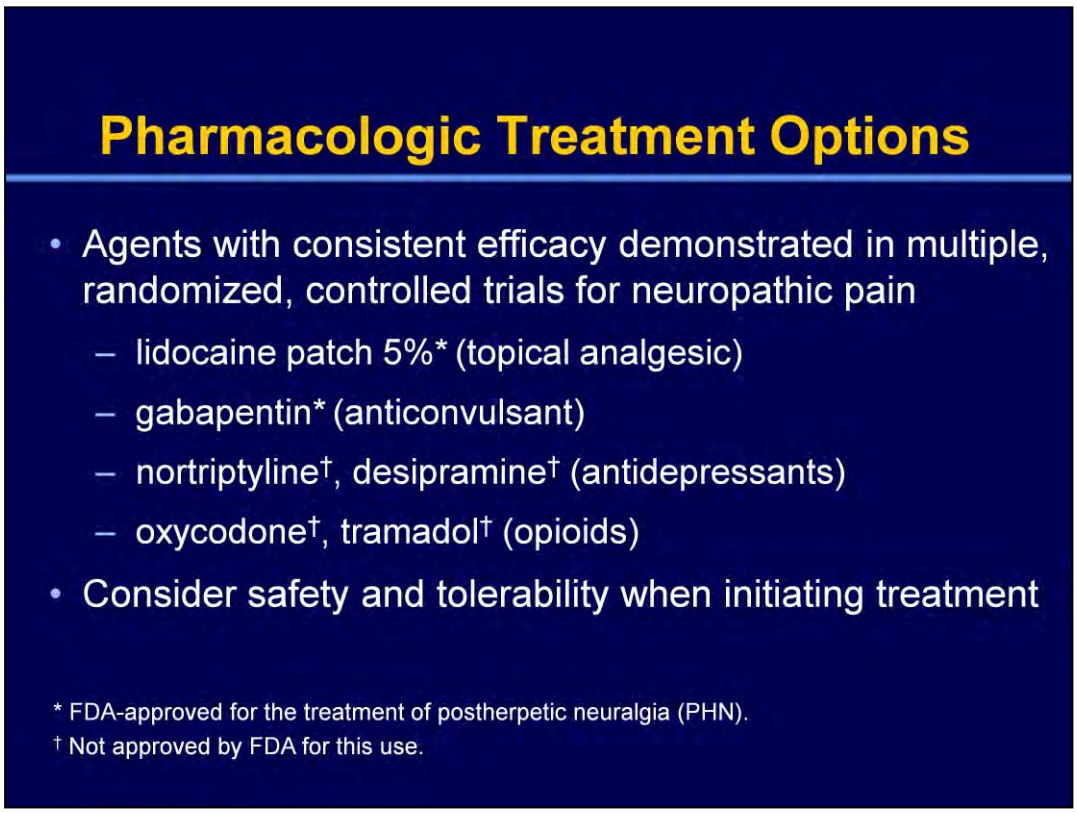
NMDA = N-methyl-D-aspartate.



- The slide lists the various treatments for neuropathic pain in order of invasiveness.[1] However, the efficacy of treatment does not necessarily match its invasiveness. For some patients, behavioral or physical therapy or a topical medication can be at least as effective as an interventional technique.[2,3]
- While there are many treatment options and combinations for neuropathic pain, this presentation will focus on those meeting three important criteria: 1) efficacy—demonstrated in controlled clinical trials; 2) safety—demonstrated in controlled clinical trials and subsequent clinical experience; 3) favorable tolerability profiles (ie, side effects, drug/drug interactions).
- Psychological/physical approaches to pain management include relaxation therapy and physical exercise programs.
- Topical medications consist of the lidocaine patch 5%, capsaicin, and a variety of custom-compounded topical agents of unknown effectiveness.[2,4]
- Oral medications include anticonvulsants such as gabapentin, tricyclic antidepressants (TCAs), opioids, and miscellaneous agents (eg, mexiletine, baclofen).[1,4]
- The two types of injections are nerve blocks and local infiltrations that are usually administered with local anesthetics and/or steroids.[5]
- The interventional techniques that require referral to a specialist are spinal cord stimulation, spinal analgesia, brain stimulation, and various neurosurgical procedures such as dorsal root entry zone lesions.[2,6]

1. Mackin GA. *J Hand Ther*. 1997;10:96-109.
2. Katz N. *Clin J Pain*. 2000;16:S41-S48.
3. Leland JY. *Geriatrics*. 1999;54:23-37.
4. Belgrade MJ. *Postgrad Med*. 1999;106:127-140.
5. Galer BS, Dworkin RH. *A Clinical Guide to Neuropathic Pain*. Minneapolis, Minn: McGraw-Hill Companies Inc; 2000:97.

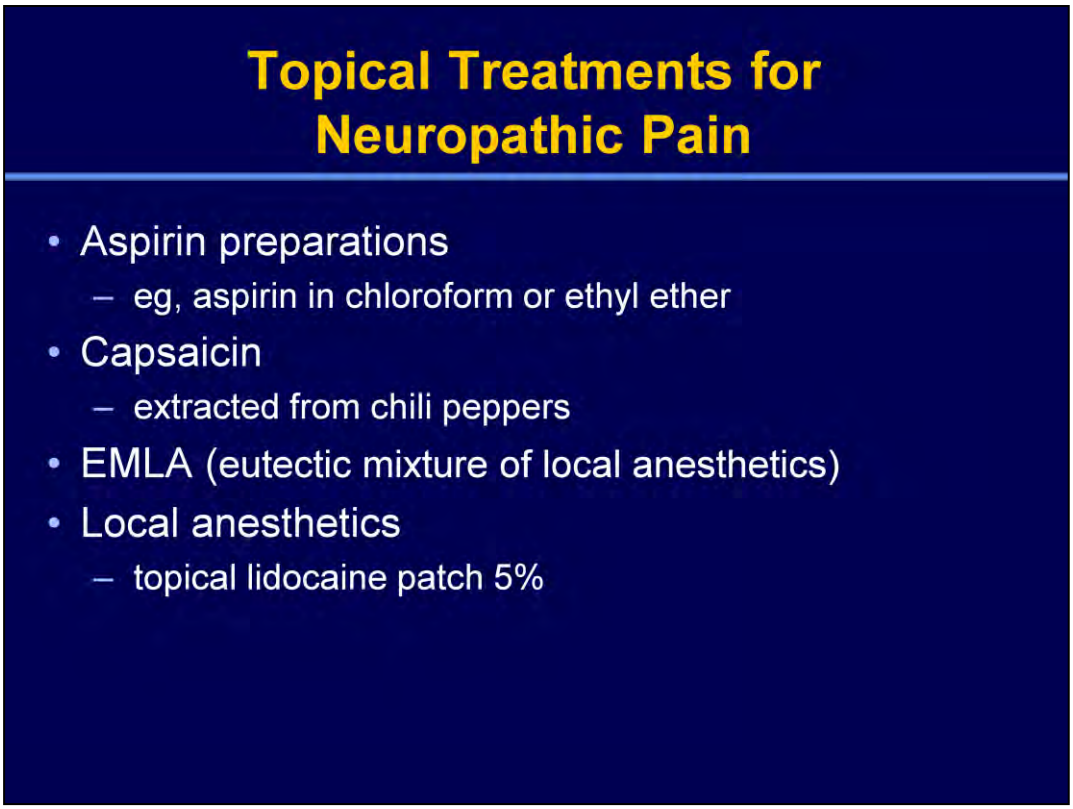
6. Gonzales GR. *Neurology*. 1995:45(suppl 9):S11-S16.



- Although there are numerous medications for the treatment of neuropathic pain, those listed on this slide have demonstrated efficacy in multiple, consistent, randomized, controlled trials. As such, these agents provide an evidence-based treatment approach for neuropathic pain and will constitute the focus of this program's discussion on pharmacologic treatment.
- When selecting a pharmacologic treatment regimen, consideration should also be given to safety and tolerability factors such as side-effect profile and potential for drug interactions. Controlled clinical trials and clinical experience document that the lidocaine patch, because of its nonsystemic mechanism of action, has the least potential for adverse side effects or drug interactions. Among systemic agents, gabapentin, which has no significant side effects, has demonstrated favorable safety and tolerability. Based on these factors, as well as being FDA-approved for the treatment of PHN, the lidocaine patch and gabapentin are often selected as initial treatments for neuropathic pain.[1-6]
- Nortriptyline, desipramine, tramadol, and controlled-release oxycodone also have demonstrated safety and tolerability profiles which are more favorable than those of earlier agents such as amitriptyline, phenytoin, carbamazepine, and others.[1,2,7-14]

1. Backonja M et al. *JAMA*. 1998;280:1831-1836.
2. Rowbotham M et al. *JAMA*. 1998;280:1837-1842.
3. Carter GT et al. *Phys Med Rehabil Clin N Am.* 2001;12:447-459.
4. Rowbotham MC et al. *Pain*. 1996;65:39-44.
5. Galer BS et al. *Clin J Pain*. 2002;18:297-301.
6. Galer BS et al. *Pain*. 1999;80:533-538.
7. Rice AS et al. *Prostaglandins Leukot Essent Fatty Acids*. 2002;66:243-256.
8. Gorson DM. *Diabetes Care*. 1998; 21:2190-2191.
9. Max MB et al. *N Engl J Med*. 1992;326:1250-1256.

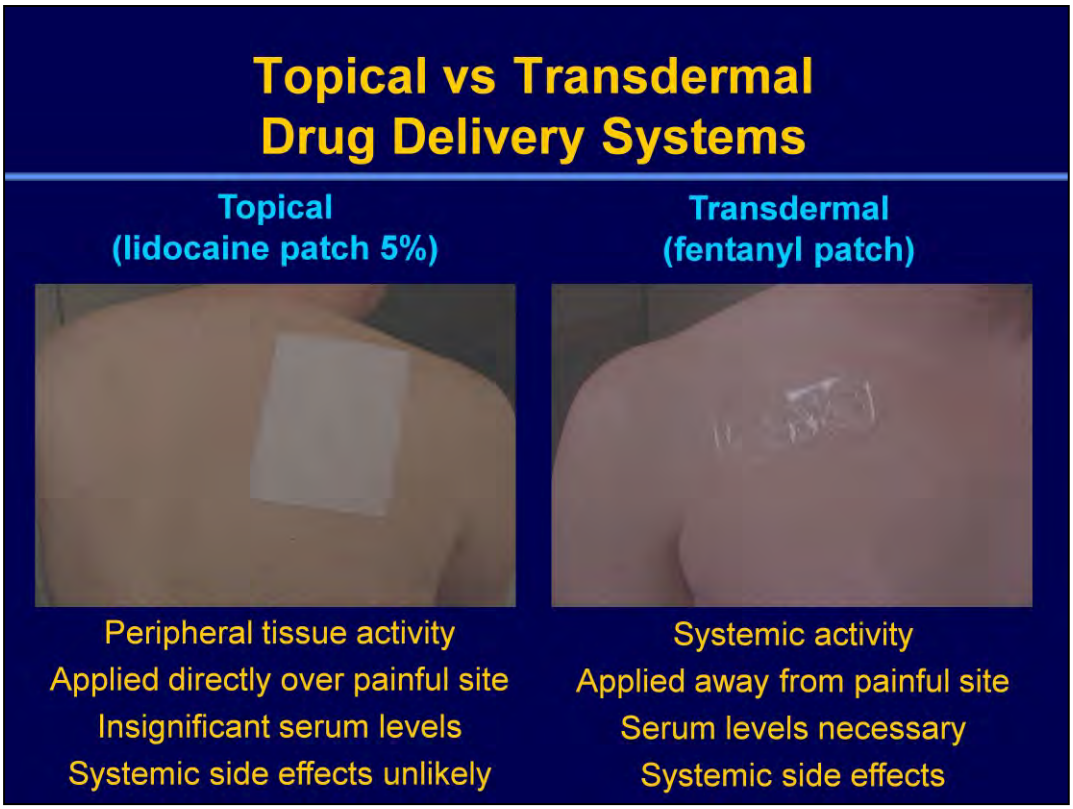
10. Watson CPN et al. *Neurology*. 1998;51:1166-1171.
11. Watson CP. *Clin J Pain.* 2000;16(suppl 2):S49-S55.
12. Watson CP et al. *Neurology*. 1998;50:1837-1841.
13. Harati Y et al. *Neurology*. 1998;50:1842-1846.
14. Sindrup SH et al. *Pain.* 1999;83:389-400.



- For many years, anecdotal reports and small, uncontrolled studies have suggested that topical preparations with aspirin may have an analgesic effect in some patients with neuropathic pain.[1] In one study, aspirin dissolved in chloroform reduced pain in 42 patients with PHN and herpes zoster.[2]
- The results of controlled trials of topical capsaicin in the treatment of neuropathic pain, including PHN and painful diabetic neuropathy, have been equivocal.[3-5] This is partially due to the difficulty of conducting a double-blind trial of capsaicin because of the associated burning it causes. This problem also limited the value of capsaicin in the clinic, because few patients can tolerate repeated applications.[3] Capsaicin is available in a number of over-the-counter formulations, including Zostrix®, Capsin, Capzasin-P™, Dolorac®, R-Gel™, Pain-X™, No Pain-HP™.
- EMLA is a eutectic mixture of the local anesthetics lidocaine and prilocaine. Clinical trial results have been mixed. In one study, repeated applications of EMLA had a variable effect on pain.[6] EMLA Anesthetic Disc® and EMLA Cream® are available but have not been approved by the FDA for treating neuropathic pain disorders.
- The topical lidocaine patch 5% (Lidoderm®) has been approved by the FDA for treating PHN on the basis of three well-controlled trials.[7-10] The effectiveness of this treatment in patients with other neuropathic pain syndromes is currently being studied; one published, open-label trial of 16 patients with refractory neuropathic pain demonstrated clinically meaningful pain relief.[11]

1. Kost RG et al. *N Engl J Med*. 1996;335:32-42; 2. King RB. *Arch Neurol*. 1993;50:1046-1053; 3. Robbins W. *Clin J Pain*. 2000;16:S86-S89; 4. Low PA et al. *Pain.* 1995;62:163-168; 5. Scheffler NM et al. *J Am Podiatr Med Assoc*. 1991;81:288-293; 6. Attal N et al. *Pain*. 1999;81:203-209; 7. Lidoderm (Endo Labs). *Physicians' Desk Reference* online. Available at: http://www.pdr.net.

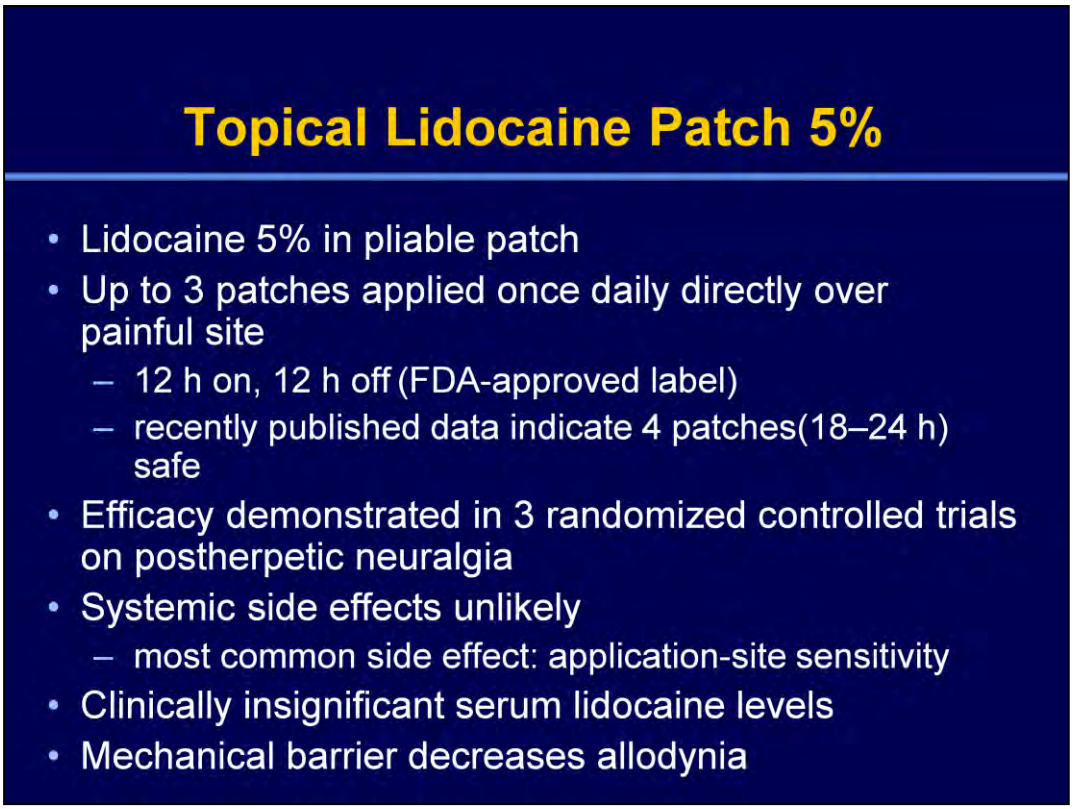
8. Rowbotham MC et al. *Ann Neurol.* 1995;37:246-253; 9. Rowbotham MC et al. *Pain.* 1996;65:39-44; 10. Galer BS et al. *Pain*. 1999;80:533-538; 11. Devers AD et al. *Clin J Pain*. 2000;16:205-208.



- Topical treatment is not the same as transdermal treatment. Topical treatment means the drug stays and acts primarily locally, with minimal systemic absorption and effects. Transdermal treatment attempts to have systemic effects by delivering the drug through the skin instead of orally, intravenously, or by other means.
- Because it is a topical agent, the lidocaine patch 5% achieves insignificant serum levels, even with chronic use. This enhances safety and makes drug interactions unlikely.[1] Clinical trials have shown no statistical difference between lidocaine patch 5% and placebo patch with regard to side effects.[2] The most common adverse event reported with the topical lidocaine patch 5% is transient minor local irritation of the skin.[3]
- Transdermal therapies for neuropathic pain include the fentanyl patch. Transdermal systems need to be applied to nonirritated skin. They deliver medication systemically, which means a slower onset of action. Patients are advised to use short-acting analgesics until analgesic efficacy with the patch is achieved.
- Because serum levels of the drug increase correlatively with duration of transdermal patch wear-time, side effects can be significant and problematic. Nausea, mental clouding, and skin irritation are commonly reported. More serious side effects include serious or life-threatening hypoventilation and bradycardia. Drug-drug interactions may also be a problem, especially concomitant use of the transdermal fentanyl patch and central nervous system (CNS) depressants (eg, benzodiazepines).[4]

1. Argoff CE. New analgesics for neuropathic pain: the lidocaine patch. *Clin J Pain*. 2000;16(2 suppl):S62-S66.
2. Galer BS, Rowbotham MC, Perander J, Friedman E. Topical lidocaine patch relieves postherpetic neuralgia more effectively than a vehicle topical patch: results of an enriched enrollment study. *Pain*. 1999;80:533-538.
3. Galer BS, Dworkin RH. *A Clinical Guide to Neuropathic Pain.* Minneapolis, Minn: McGraw-Hill

Companies Inc; 2000:61-64.
4. Duragesic [package insert]. Titusville, NJ: Janssen Pharmaceutica; 1999.

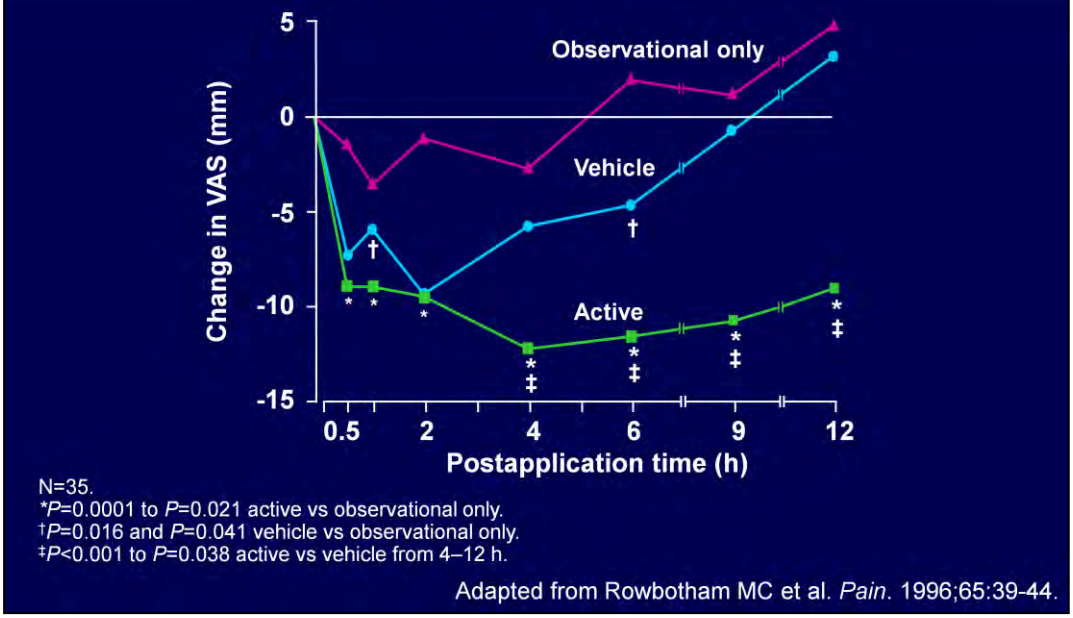


- The topical lidocaine patch, the first drug with an FDA-approved indication for PHN, provides an effective treatment option with minimal side effects.
- The topical lidocaine patch 5% is a pliable 10 cm x 14 cm patch. The lidocaine patch 5% can be affixed directly to the affected areas. Multiple patches may be used to treat multiple painful sites or the patch may be trimmed. Up to three patches may be applied to intact skin for up to 12 hours within a 24-hour period.[1] In a recent study in which four patches were used for 3 days plasma lidocaine concentrations were well below those associated with either cardiac arrythmias or toxicity (mean C_{max} at steady state with lidocaine patches applied QD and bid was 186 ng/mL and 225 ng/mL, respectively; AUCss was reported at 3,550 ng*h/mL and 2,253 ng*h/mL for the QD and bid dosing groups, respectively).[2]
- The efficacy of the lidocaine patch 5% has been demonstrated in three randomized vehicle-controlled trials.[3-5] The patch is indicated for treatment of PHN.[1]
- Because it is a topical agent, the lidocaine patch 5% achieves insignificant serum levels, even with chronic use. This enhances safety.[6-9] Clinical trials have shown no statistical difference between lidocaine patch 5% and placebo patch with regard to side effects.[5] The most common adverse event reported with the topical lidocaine patch 5% is transient minor local irritation of the skin.[7]
- In one clinical trial of patients treated with the vehicle patches, data suggest that the patch provides a mechanical barrier to the stimuli that cause allodynia.[4]

1. Lidoderm (lidocaine patch 5%) [package insert]; 2. Alvarez NA et al. In: *Programs and Abstracts of the IASP 10th World Congress on Pain*. 2002. Abstract 175-P171; 3. Rowbotham MC et al. In: *Programs and Abstracts of the 8th World Congress on Pain - Abstracts*. 1996. 274;
4. Rowbotham MC et al. *Pain*. 1996;65:39-44; 5. Galer BS et al. *Pain*. 1999;80:533-538;
6. Argoff CE. *Clin J Pain*. 2000;16(2 suppl):S62-S66; 7. Galer BS et al. *A Clinical Guide to Neuropathic Pain.* 2000:61-64; 8. Gammaitoni AR et al. *Ann Pharmacother.* 2002;36:236-240;

9. Gammaitoni A et al. *J Pain*. 2002;3(suppl 1):52.

Efficacy of Lidocaine Patch 5% in Postherpetic Neuralgia

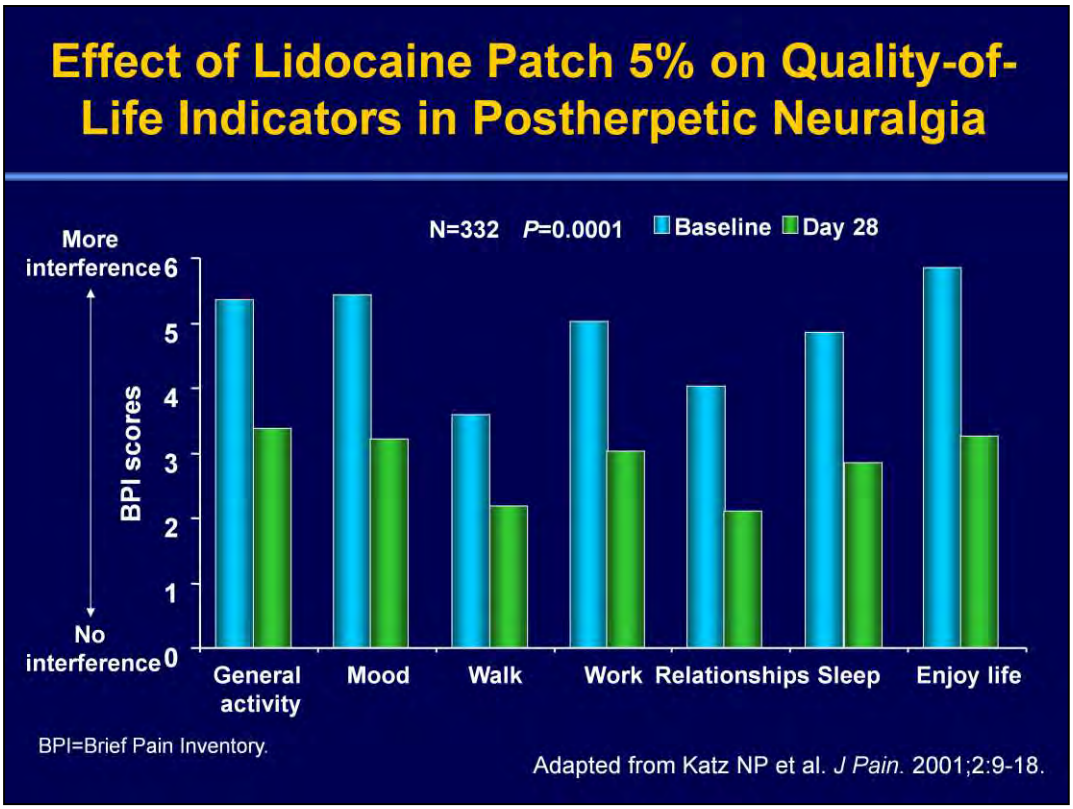


N=35.
*P=0.0001 to P=0.021 active vs observational only.
†P=0.016 and P=0.041 vehicle vs observational only.
‡P<0.001 to P=0.038 active vs vehicle from 4–12 h.

Adapted from Rowbotham MC et al. *Pain*. 1996;65:39-44.

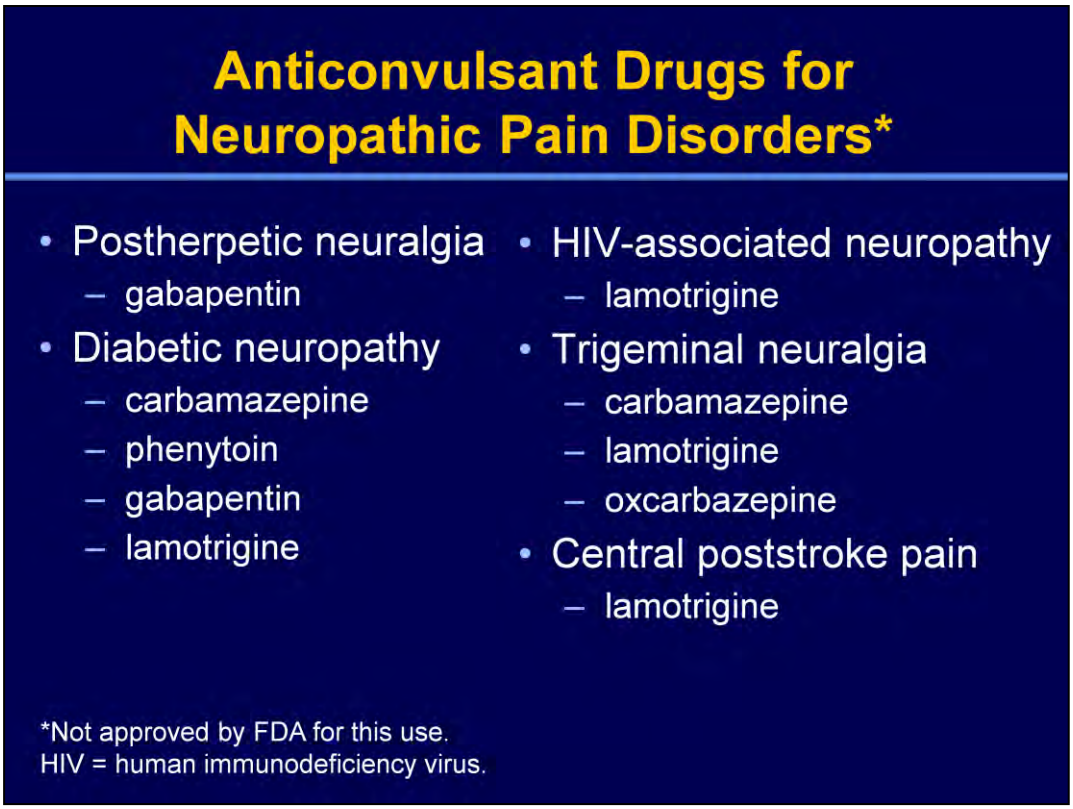
- The initial study that led to FDA approval of the lidocaine patch 5% was conducted by Rowbotham and colleagues in 35 subjects with PHN with allodynia. Subjects reported the severity of their pain on a 100-mm visual analog scale (VAS) at baseline and following the application of patches that either did (active) or did not (vehicle control) contain lidocaine.
- Mean pretreatment VAS scores ranged from 47.2 to 49.3 mm. As shown in the slide, the active patch provided a significantly greater reduction in VAS pain score than the vehicle patch at 4, 6, 9, and 12 hours after application (P<0.001 to P=0.038).
- The vehicle patch, which was superior to "observational only" at 1 and 6 hours (individual time points P=0.016 and P=0.041), had an apparently short-lived effect, which was presumably due to the mechanical barrier provided by the patch. The vehicle patch resembles the lidocaine patch 5%, but it does not contain the active ingredient and was used as a placebo in this trial.
- The researchers concluded that the results of the study support the use of topical local anesthetic patches as a potentially significant treatment modality for PHN.

Rowbotham MC, Davies PS, Verkempinck C, Galer BS. Lidocaine patch: double-blind controlled study of a new treatment method for post-herpetic neuralgia. *Pain*. 1996;65:39-44.



- The effect of the lidocaine patch 5% on QOL indicators in 332 patients with PHN persisting or starting at least 1 month from the onset of herpes zoster was evaluated in a multicenter, open-label study.
- In this study, the short form of the Brief Pain Inventory (BPI) was administered to patients. This measure includes 0-to-10 numeric rating scales of seven important domains of QOL.
- These QOL measures include general activity, mood, walk, work, relationships, sleep, and the ability to enjoy life.
- As shown in the slide, treatment with the lidocaine patch 5% produced significant improvement in these BPI scores at day 28, compared with baseline values for all seven QOL measures (*P*=0.0001 for all changes from baseline).

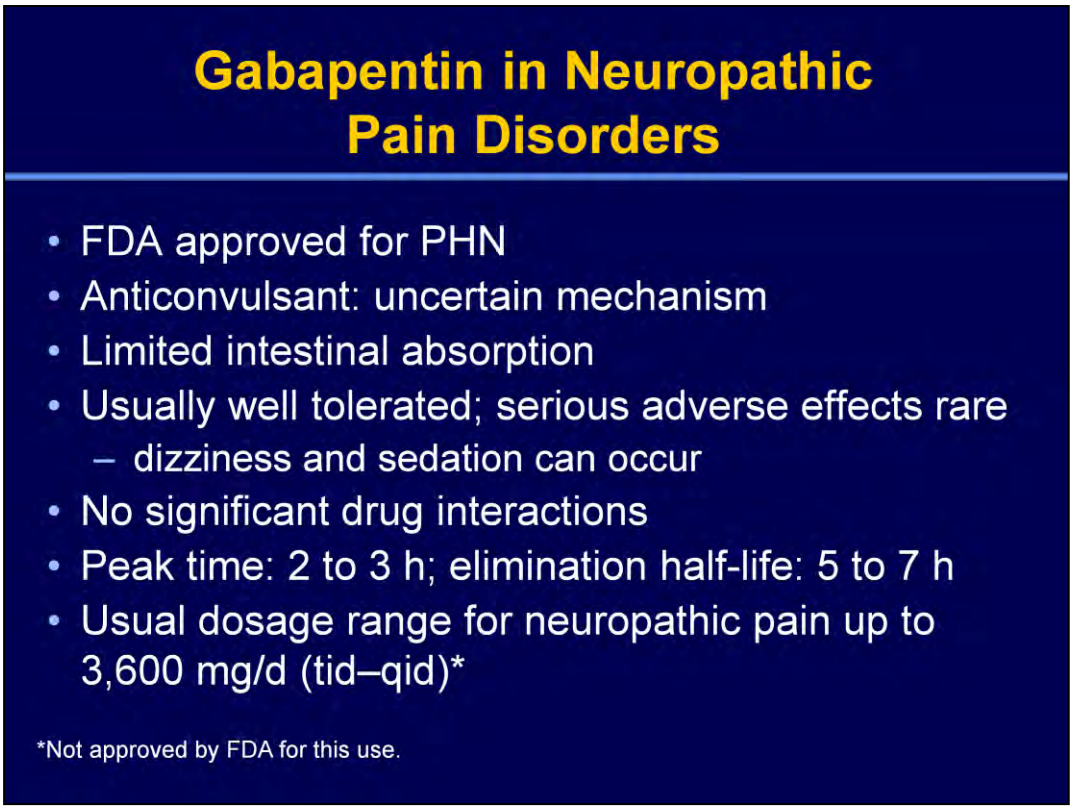
Katz NP, Davis MW, Dworkin RH. Topical lidocaine patch produces a significant improvement in mean pain scores and pain relief in treated PHN patients: results of a multicenter open-label trial. *J Pain*. 2001;2:9-18.



- Anticonvulsant medications have been used in the treatment of neuropathic pain for many years without FDA approval (except for carbamazepine's indication for trigeminal neuralgia). The slide provides a summary of many of the controlled trials that have been conducted examining the efficacy of anticonvulsant drugs in the treatment of various neuropathic pain syndromes.[1-7]
- The studies of carbamazepine and phenytoin conducted in the 1960s and 1970s do not meet today's standards of methodological rigor.[8] The phenytoin studies have produced both successful and unsuccessful results.[9]
- The two studies of gabapentin are among the largest clinical trials of the treatment of neuropathic pain ever conducted.[8,10] These studies have stimulated a great deal of clinical and research interest in the efficacy and mechanisms of action of anticonvulsant drugs in treating patients with neuropathic pain.
- First-generation anticonvulsant drugs, which include carbamazepine and phenytoin, sometimes provoke serious side effects and drug-drug interactions that do not occur with second-generation anticonvulsants.[11] We will be focusing on gabapentin because it is the anticonvulsive most commonly used for neuropathic pain and for which there is the most clinical data.

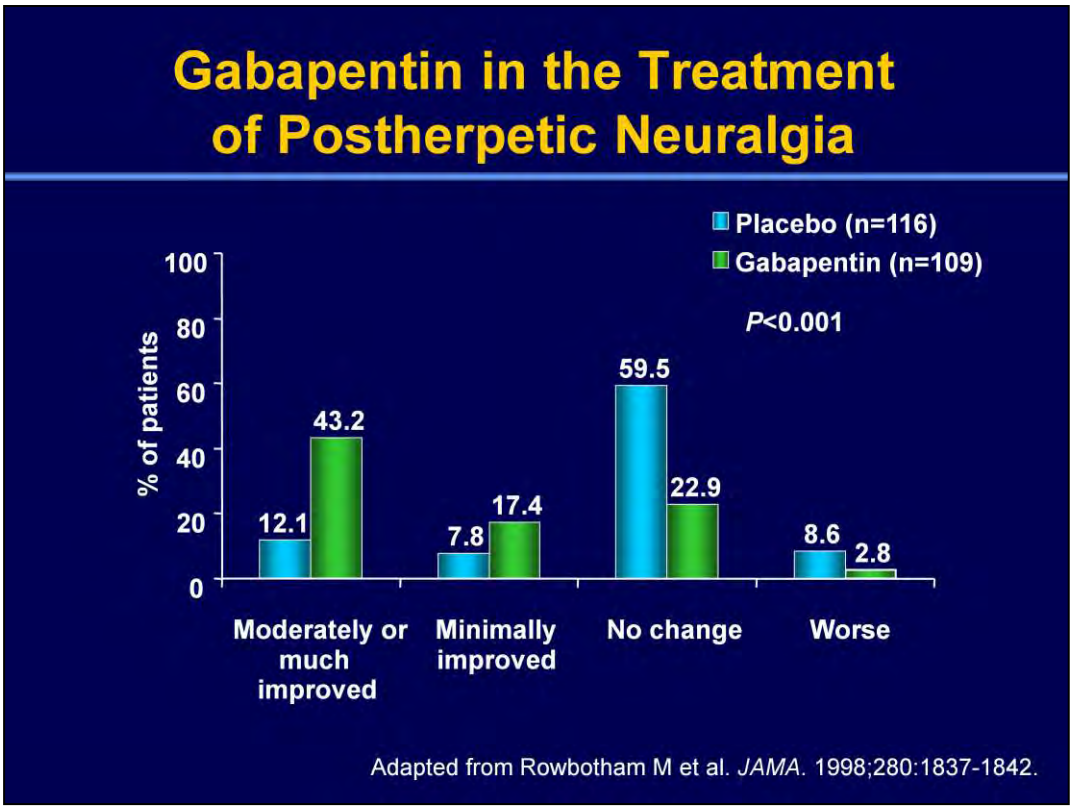
1. Rowbotham M et al. *JAMA*. 1998;280:1837-1842; 2. Eisenberg E et al. *Neurology*. 2001;57: 505-509; 3. Simpson DM et al. *Neurology*. 2000;54:2115-2119; 4. Campbell FG et al. *J Neurol Neurosurg Psychiatry*. 1966;29:265-267; 5. Zakrzewska JM et al. *Pain*. 1997;73:223-230; 6. Zakrzewska JM et al. *J Neurol Neurosurg Psychiatry*. 1989;52:472-476; 7. Vestergaard K et al. *Neurology*. 2001;56:184-190; 8. Rull J et al. *Diabetologia*. 1969;5:215-218; 9. Chadda VS et al.

J Assoc Physicians India. 1978;26:403-406; 10. Backonja M et al. *JAMA*. 1998;280:1831-1836;
11. Ross EL. *Neurology*. 2000;55:S41-S46.



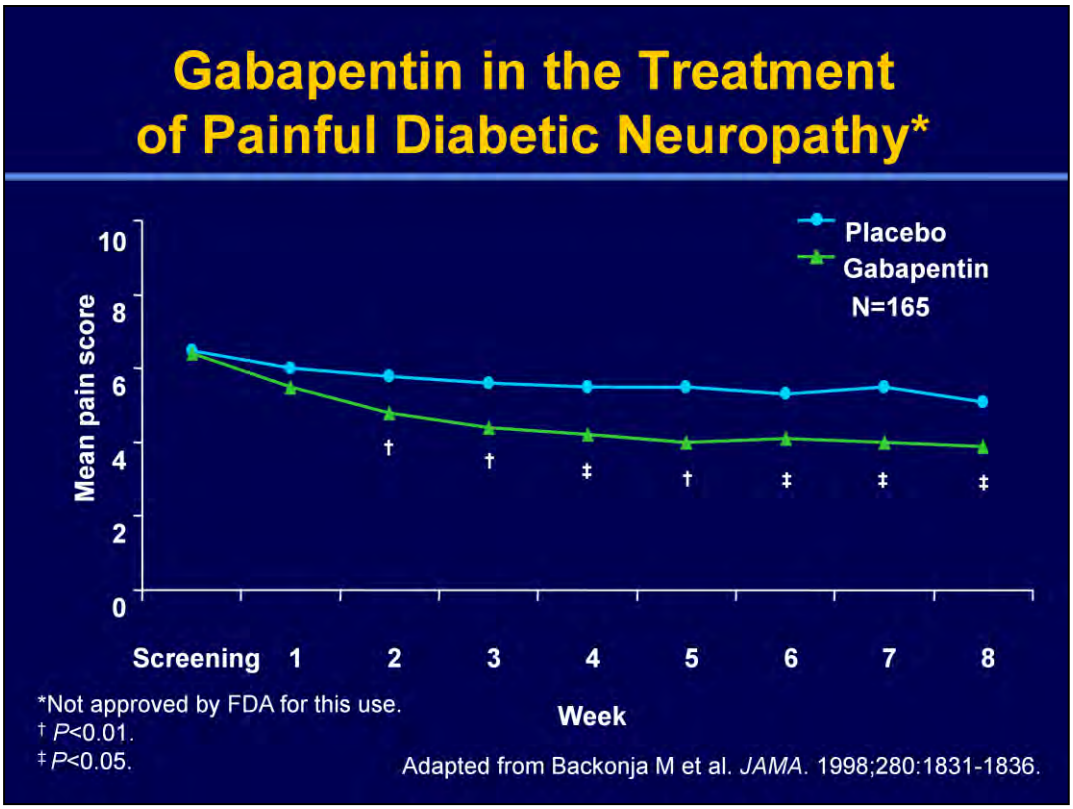
- Gabapentin is an anticonvulsant which has recently been approved for the treatment of PHN, but it does not have FDA approval for this indication.[1]
- Its mechanism of action has not been completely identified.
- Gabapentin has limited intestinal absorption and is usually well tolerated. Among the more common adverse events associated with its use are dizziness and sedation. It has rare serious adverse effects.
- No clinically significant drug-drug interactions are known.
- The time to peak concentration is 2 to 3 hours, and the elimination half-life is 5 to 7 hours. Plasma clearance, however, decreases in elderly patients and in patients with impaired renal function.[2]
- The effective dose for adjunctive therapy of partial seizures with or without secondary generalization in adults with epilepsy is 900 to 1,800 mg/day, given in divided doses tid and titrated over 3 days.[2] For pain, clinical experience has shown that much higher doses are often necessary and well tolerated; the usual dosage range is up to 3,600 mg/day (tid-qid).[1]

1. Backonja M-M. Anticonvulsants (antineuropathics) for neuropathic pain syndromes. *Clin J Pain*. 2000;16:S67-S72.
2. Neurontin (gabapentin) [package insert]. Morris Plains, NJ: Parke-Davis; 1999.



- Rowbotham and colleagues conducted a large, multicenter, randomized, double-blind, placebo-controlled clinical trial of gabapentin for the treatment of PHN in 229 patients.
- Patients received 8 weeks of treatment with either gabapentin, titrated to a maximum of 3,600 mg/day, or matching placebo.
- Patients' global impression of change, one of the study's outcomes, is shown on the slide for week 8 of the study or at the patient's final study visit.
- The percentage of patients treated with gabapentin who reported themselves on the Subjects Global Impression of Change as improved at the end of treatment was significantly greater than the corresponding percentage of patients treated with placebo.
- In addition, at the final week of therapy, patients treated with gabapentin had a statistically significant reduction (determined by means of an intent-to-treat analysis) in average daily pain score from 6.3 to 4.2 points, compared with a decline from 6.5 to 6.0 points in subjects receiving placebo ($P<0.001$).

Rowbotham M, Harden N, Stacey B, et al, for the Gabapentin Postherpetic Neuralgia Study Group. Gabapentin for the treatment of postherpetic neuralgia: a randomized controlled trial. *JAMA*. 1998;280:1837-1842.



- Backonja and colleagues reported the results of a randomized, double-blind, placebo-controlled clinical trial of the anticonvulsant gabapentin for the treatment of pain associated with diabetic peripheral neuropathy.
- Patients received 8 weeks of treatment with either gabapentin, titrated to 3,600 mg/day or maximum tolerated dosage, or a matching placebo.
- The primary efficacy measure was mean daily pain severity measured on the 11-point Likert scale, with a 0-to-10 numeric rating scale (0 indicating no pain and 10 indicating worst possible pain).
- As indicated on the slide, patients who received gabapentin had significantly less pain at weeks 2 through 8 than did those who received placebo.

Backonja M, Beydoun A, Edwards KR, et al, for the Gabapentin Diabetic Neuropathy Study Group. Gabapentin for the symptomatic treatment of painful neuropathy in patients with diabetes mellitus: a randomized controlled trial. *JAMA*. 1998;280:1831-1836.

Gabapentin: Improvement in Quality of Life for Postherpetic Neuralgia

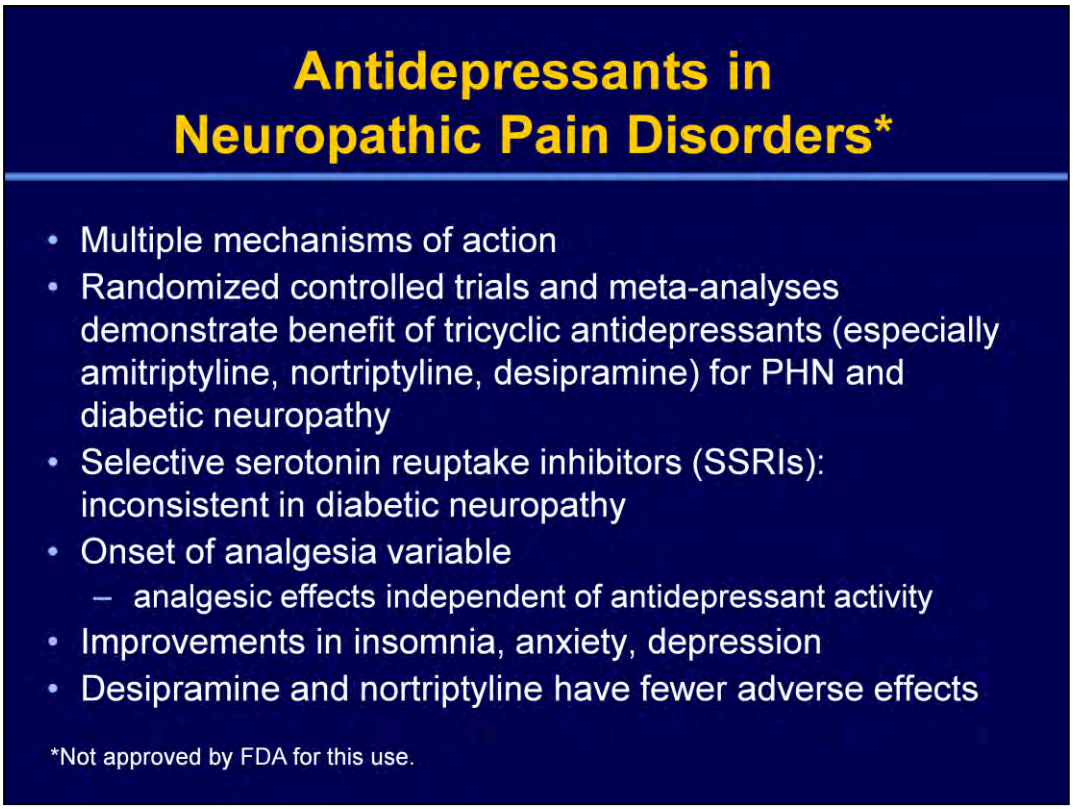
	Baseline Mean	Week 8 Mean	*P*	Mean Change From Baseline
Physical Functioning				
Gabapentin	61.7	66.2	0.01	4.5
Placebo	57.6	57.5		-0.1
Bodily Pain				
Gabapentin	42.9	57.4	<0.001	14.5
Placebo	42.7	47.3		4.7
Mental Health				
Gabapentin	67.9	74.6	<0.001	6.7
Placebo	69.2	69.9		0.7
Total Mood Disturbance				
Gabapentin	31.9	16.9	<0.001	-15.0
Placebo	30.6	27.7		-2.9

N=229.

Adapted from Rowbotham M et al. *JAMA*.1998;280:1837-1842.

- Rowbotham and colleagues administered gabapentin or placebo to 229 patients with PHN in a randomized, double-blind, placebo-controlled clinical trial conducted at 16 medical centers.
- Gabapentin was titrated over 4 weeks to a maximum dosage of 3,600 mg/day. Treatment was continued for an additional 4 weeks at the maximum tolerated dosage.
- One of the secondary efficacy endpoints was patient QOL and mood states, as measured by the Short Form-36 (SF-36) Quality of Life Questionnaire and the Profile of Mood States (POMS).
- This slide lists three of the SF-36 indicators (physical functioning, bodily pain, and mental health) and one POMS measure (total mood disturbance) on which patients receiving gabapentin had significantly better improvements than did patients receiving placebo.
- Gabapentin produced significantly greater improvements on other measures than did placebo ($P<0.01$). These included (for SF-36) role-physical and vitality, and (for POMS) depression-dejection, anger-hostility, fatigue-inertia, and confusion-bewilderment.

Rowbotham M, Harden N, Stacey B, et al, for the Gabapentin Postherpetic Neuralgia Study Group. Gabapentin for the treatment of postherpetic neuralgia: a randomized controlled trial. *JAMA*. 1998;280:1837-1842.



- Tricyclic antidepressants (TCAs) act in part by inhibiting the reuptake of norepinephrine and serotonin into presynaptic neurons. They have been used to relieve neuropathic pain, although this indication has not been approved by the FDA.
- However, many controlled clinical trials and meta-analyses have demonstrated that TCAs (eg, imipramine, amitriptyline, desipramine, nortriptyline, clomipramine) can significantly reduce the pain of diabetic neuropathy and PHN.[1-4]
- Some, but not all, selective serotonin reuptake inhibitors (SSRIs) have also been shown to be effective for neuropathic pain. Paroxetine and citalopram (slightly) have shown benefit for diabetic neuropathy,[1,2] while fluoxetine has proved to be no more effective than placebo.[3] In general the SSRIs are felt to be, at best, inconsistently effective for neuropathic pain.[4]
- Some patients who receive antidepressants for neuropathic pain may experience improvement in insomnia, anxiety, and depression.[4,5] Onset of analgesia with antidepressants generally occurs before the onset of the antidepressant effect. The pain-relieving effect of antidepressant agents appears to be independent of their antidepressant effect.[4] Selective norepinephrine reuptake inhibitors (SNRIs) are to be explored for use in neuropathic pain.
- This module will focus on desipramine and nortriptyline because they are the two antidepressants most commonly used for treatment of neuropathic pain and for which there is the most clinical data.[6-8]

1. Sindrup SH et al. *Pain*. 1990;42:135-144; 2. Sindrup SH et al. *Clin Pharmacol Ther*. 1992;52: 547-552; 3. Max MB et al. *N Engl J Med*. 1992;326:1250-1256; 4. Galer BS et al. *A Clinical Guide to Neuropathic Pain*. 2000:71-72,93; 5. Pappagallo M. *Rheum Dis Clin N Am*. 1999;25:193-209; 6. Max MB et al. *Neurology*. 1988;38:1427-1432; 7. Watson CP at al. *Neurology*. 1998;51:1166-1171; 8. Kishore-Kumar R et al. *Clin Pharmacol Ther*. 1990;47:305-312.

Antidepressants*

Tricyclic	SSRI	Other
Amitriptyline (Elavil®)	Fluoxetine (Prozac®)	Nefazodone (Serzone®)
Desipramine (Norpramin®)	Paroxetine (Paxil®)	Venlafaxine (Effexor®)
Doxepin (Sinequan®)	Sertraline (Zoloft®)	Trazodone (Desyrel®)
Imipramine (Tofranil®)	Fluvoxamine (Luvox®)	Bupropion (Wellbutrin®)
Nortriptyline (Pamelor®)		

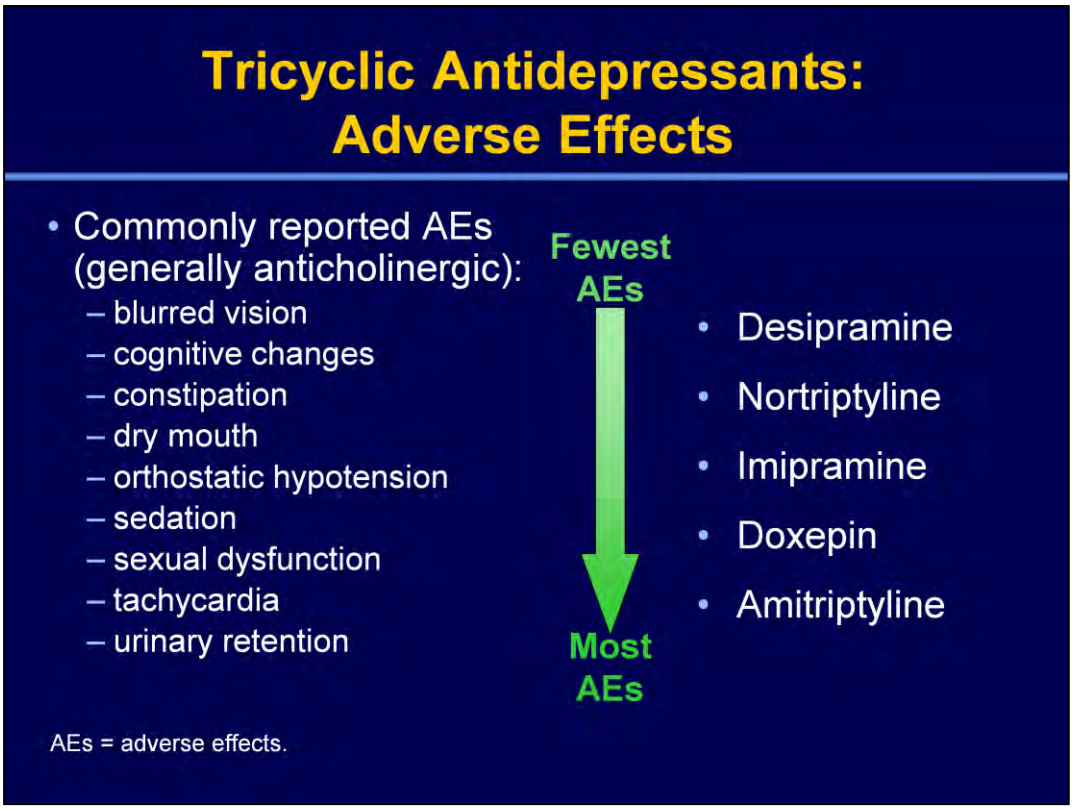
*Partial list.

Review of Antidepressant Analgesia

Meta-analysis by Onghena (1992)		Synthesis by Magni (1991)	
Diagnosis	**No. of Studies**	**Effect Size**	
Diabetic neuropathy	1	1.71	Responsive
PHN	2	1.44	Responsive
Tension headache	6	1.11	Responsive
Migraine	4	0.82	Responsive

Review of Antidepressant Analgesia (cont)

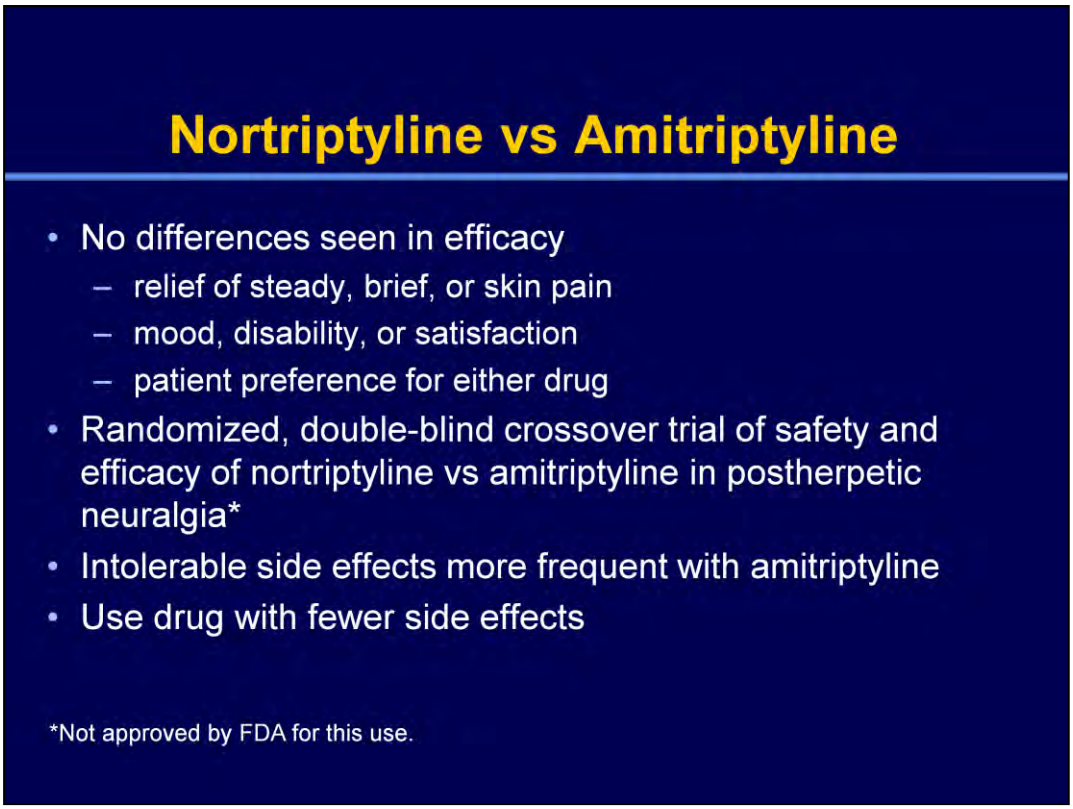
Meta-analysis by Onghena (1992)		Synthesis by Magni (1991)	
Diagnosis	**No. of Studies**	**Effect Size**	
Atypical facial pain	3	0.81	Responsive
Chronic back pain	5	0.64	Minimal clinical benefit
Rheumatological pain	10	0.37	Fibrositis responsive; Osteo- and rheumatoid arthritis probably responsive
Not specified or mixed	7	0.23	Probable effect



- Adverse effects commonly reported with TCAs are anticholinergic effects, which are listed on the left side of the slide. The adverse effects include blurred vision, cognitive changes (such as concentration, memory loss, and confusion), constipation, dry mouth, orthostatic hypotension, sedation, tachycardia, and urinary retention. All TCAs are reported to cause these adverse events in varying degrees of frequency and severity.[1,2]
- The TCA agents listed on the right side of the slide are organized in descending order of adverse effects, starting with desipramine (fewest adverse effects), nortriptyline, imipramine, doxepin, and amitriptyline (most adverse effects).[2,3]
- Because of the potential for adverse events and outcomes, amitriptyline should not be prescribed for people older than 65 years. Desipramine would be more appropriate for this population. Of all the drugs that are inappropriate for the elderly, amitriptyline is one of most frequently prescribed.[4]
- Because the TCAs appear to be almost equally efficacious, a rational approach for clinical practice is to start with the agents with the fewest adverse effects, unless a specific “side effect,” such as nighttime sedation, is desired.

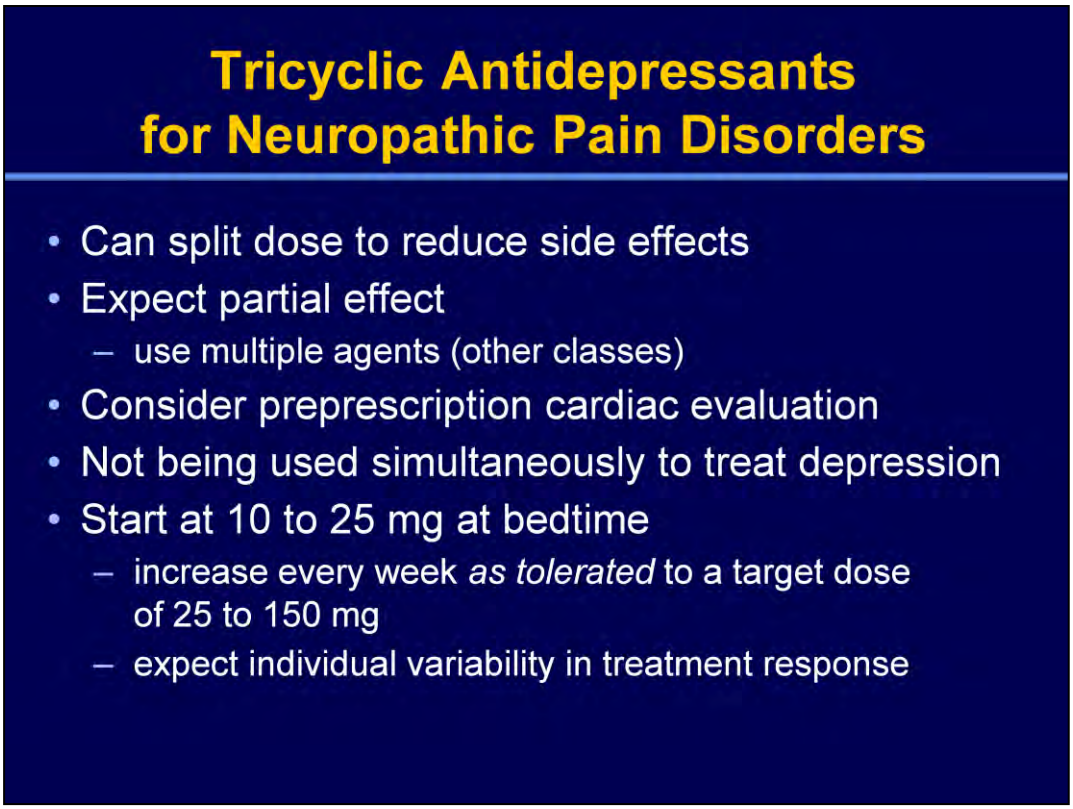
1. Rowbotham MC, Petersen KL, Davies PS, et al. Recent developments in the treatment neuropathic pain. *Proceedings of the 9th World Congress on Pain*. Seattle, Wash: IASP Press; 2000:833-855.
2. Mackin GA. Medical and pharmacologic management of upper extremity neuropathic pain syndromes. *J Hand Ther*. 1997;10:96-109.
3. Tunali D, Jefferson JW, Greist JH. *Depression and Antidepressants: A Guide*. Madison, Wis: Information Centers, Madison Institute of Medicine; 1999.
4. Piecoro LT, Browning SR, Prince TS, et al. Database analysis of potentially inappropriate drug

use in an elderly Medicaid population. *Pharmacotherapy*. 2000;20:221-228.



- Numerous randomized controlled trials of amitriptyline have established its efficacy in treating neuropathic pain, especially PHN and painful diabetic neuropathy.[1,2]
- Amitriptyline is, however, poorly tolerated by many patients because of its side effects, especially that of sedation.[1] Watson and colleagues conducted a randomized, double-blind crossover trial that compared the efficacy of nortriptyline (a better-tolerated TCA) with that of amitriptyline in 33 patients with PHN.[3] The patients had a median duration of pain of 13 months, with a combination of steady pain and brief paroxysmal pain. Patients were randomized to 5 weeks of treatment with one drug, followed by a 2-week washout period and then therapy with the other drug.
- No significant differences were found between the drugs in relieving three types of postherpetic pain: steady pain, brief pain, and pain on nonnoxious stimulation of the skin. The two pharmaceuticals produced an equally beneficial (no pain or mild pain) response in half of the patients. No differences were found in patient estimates of pain relief.[3]
- Patients who took amitriptyline reported a higher number of intolerable side effects (16) than did patients who took nortriptyline (10).[3]

1. Max MB, Lynch SA, Muir J, et al. Effects of desipramine, amitriptyline, and fluoxetine in diabetic neuropathy. *N Engl J Med*. 1992;326:1250-1256.
2. Max MB, Schafer SC, Culnane M, et al. Amitriptyline, but not lorazepam, relieves postherpetic neuralgia. *Neurology*. 1988;38:1427-1432.
3. Watson CPN, Vernich L, Chipman M, Reed K. Nortriptyline versus amitriptyline in postherpetic neuralgia. A randomized trial. *Neurology*. 1998;51:1166-1171.



- Different TCAs have different potencies, therefore significant interindividual variability exists in the efficacy, tolerability, and correct dosage of TCAs. Treatment can be initiated with a dose of 10 mg if there is increased concern about side effects. Because several weeks may be needed before benefits are realized, titration can be a slow and frustrating process. There are no shortcuts, and physicians should set appropriate expectations with the patient.[1-5]
- A cardiac evaluation should be considered for patients older than 45 years before they are given a prescription.[1]

1. Galer BS, Dworkin RH. *A Clinical Guide to Neuropathic Pain*. Minneapolis, Minn: McGraw-Hill Companies Inc; 2000:55.
2. Davis JL, Gerich JE, Schultz TA. Peripheral diabetic neuropathy treated with amitriptyline and fluphenazine. *JAMA*. 1977;238:2291-2292.
3. Belgrade MJ. Following the clues to neuropathic pain. *Postgrad Med*. 1999;106:127-140.
4. Galer BS. Neuropathic pain of peripheral origin: advances in pharmacologic treatment. *Neurology*. 1995;45(suppl 9):S17-S25.
5. Portenoy RK, Kanner RM, eds. *Pain Management: Theory and Practice*. Philadelphia, Pa:

FA Davis; 1996.

- Opioid therapy entails a number of risks for patients, but these potential problems can be prevented or circumvented.
- Titration of opioid analgesics should be based on optimizing therapeutic efficacy while minimizing side effects. Regimens of fixed doses are generally preferred over prn regimens.[1]
- Documentation is critical and should include the initial evaluation, substance abuse history, psychosocial issues, pain/pain relief, side effects, functional outcomes, and continuing monitoring. Regular discussions with family members about the patient's condition and use of opioids can improve the accuracy of monitoring.[1]
- The laws on patient monitoring vary from state to state, but the federal government regulates and legislates the use of controlled substances and drugs. Generally, federal laws have priority over state laws.[2]
- Most opioid side effects can be controlled with appropriate specific management (eg, prophylactic bowel regimen, use of stimulants).[3]
- Patients on opioids or those who appear to require them also have significant psychosocial rehabilitative issues and are generally best referred to a multidisciplinary center with experience managing chronic pain with opioids.[1]
- Addiction is referred to by many as psychological dependence.

1. Pappagallo M. Aggressive pharmacologic treatment of pain. *Rheum Dis Clin N Am*. 1999;25:193-213.

2. Clark HW. Policy and medical-legal issues in the prescribing of controlled substances. *J Psychoactive Drugs*. 1991;23:321-328.
3. Zenz M. Morphine myths: sedation, tolerance, addiction. *Postgrad Med J*. 1991;67:S100-S102.

Opioid Efficacy Studies in Neuropathic Pain Disorders

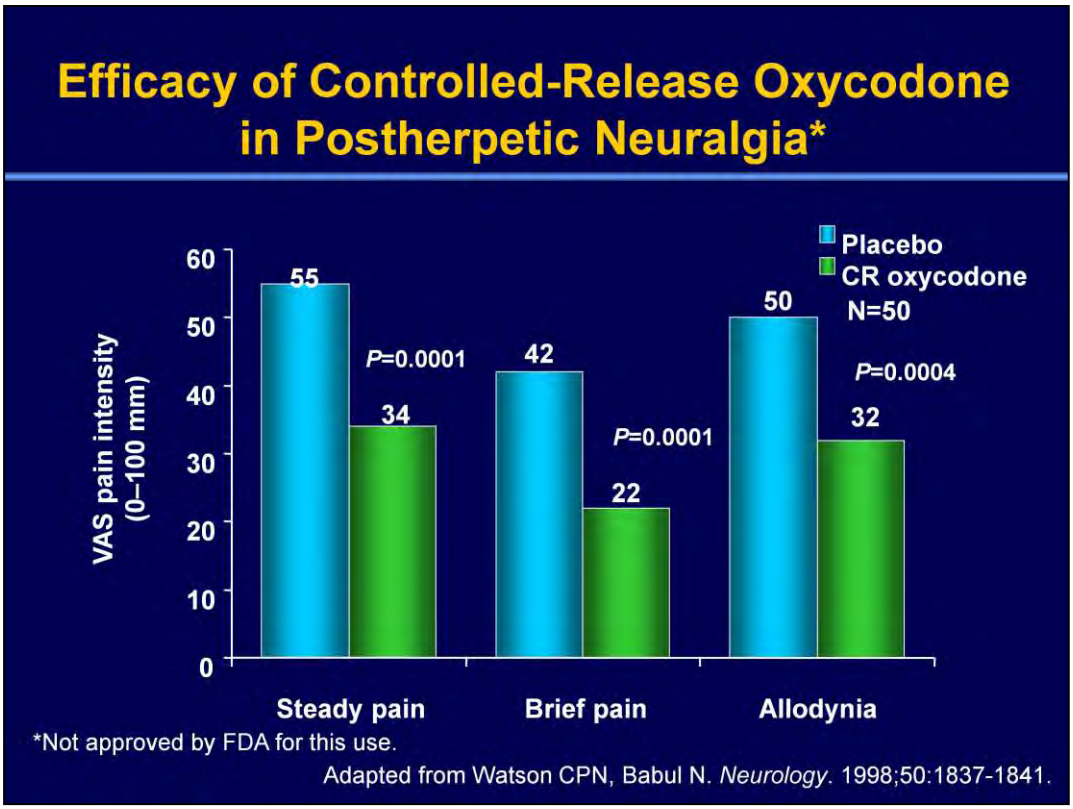
- Nonmalignant neuropathic pain disorders
  - IV fentanyl
- Postherpetic neuralgia
  - IV morphine
  - controlled-release oxycodone
- Phantom limb pain
  - oral morphine
- Diabetic neuropathy
  - tramadol
  - oxycodone

IV = intravenous.

- Trade names for commonly available opioids include Duragesic® (fentanyl); Duramorph®, Infumorph®, MS Contin®, Oramorph®, and Roxanol® (morphine); Oxycontin® (controlled-release oxycodone); and Ultram® (tramadol).
- Studies by Dellemijn and Vanneste, and Rowbotham et al investigated the effectiveness of intravenous (IV) fentanyl and morphine against nonmalignant neuropathic pain and PHN.[1,2]
  - In the Dellemijn and Vanneste study, fentanyl's beneficial effect did not vary with the type of neuropathic pain, which included PHN, radiculopathy, posttraumatic nerve pain, and other types of pain. Fentanyl relieved pain intensity and unpleasantness equally, but a comparison drug, diazepam, and placebo did not decrease either pain measurement.[1]
  - In the Rowbotham and colleagues study, IV morphine administered with IV lidocaine reduced pain intensity. Allodynia disappeared in patients who reported pain relief.[2]
- The Watson and Babul study demonstrated that controlled-release oxycodone (CR oxycodone) significantly (P=0.0001) decreased pain from PHN without causing serious adverse effects.[3,4] Studies documenting long-term efficacy, however, have not been conducted.
- The small (N=12) double-blind crossover study conducted by Huse et al found that morphine, but not placebo, produced a significant (P<0.01) reduction in phantom limb pain. A pain reduction of more than 50% occurred in 42% of patients receiving morphine, which may also influence cortical reorganization.[5]
- In a study of 131 patients with diabetic neuropathy, tramadol was significantly more effective (P<0.001) than placebo in treating pain.[6] Patients in the tramadol group also scored significantly better in physical (P=0.02) and social functioning (P=0.04).

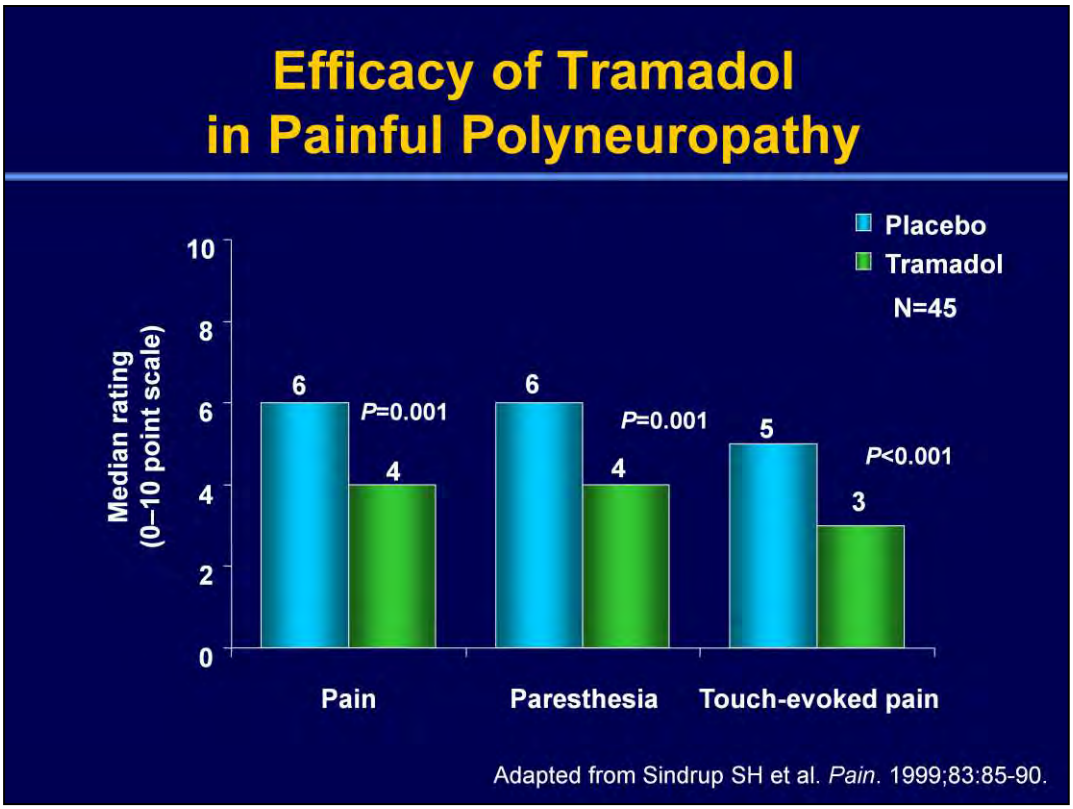
1. Dellemijn PLI et al. *Lancet*. 1997;349:753-758; 2. Rowbotham MC et al. *Neurology*.1991; 41:1024-1028; 3. Watson CPN et al. *Neurology*. 1998;50:1837-1841; 4. Watson C et al. In: *Program and abstracts of the IASP 10th World Congress on Pain*. 2001. Abstract 1300-P216.

5. Huse E et al. *Pain*. 2001;90:47-55; 6. Harati Y et al. *Neurology*. 1998;50:1842-1846.



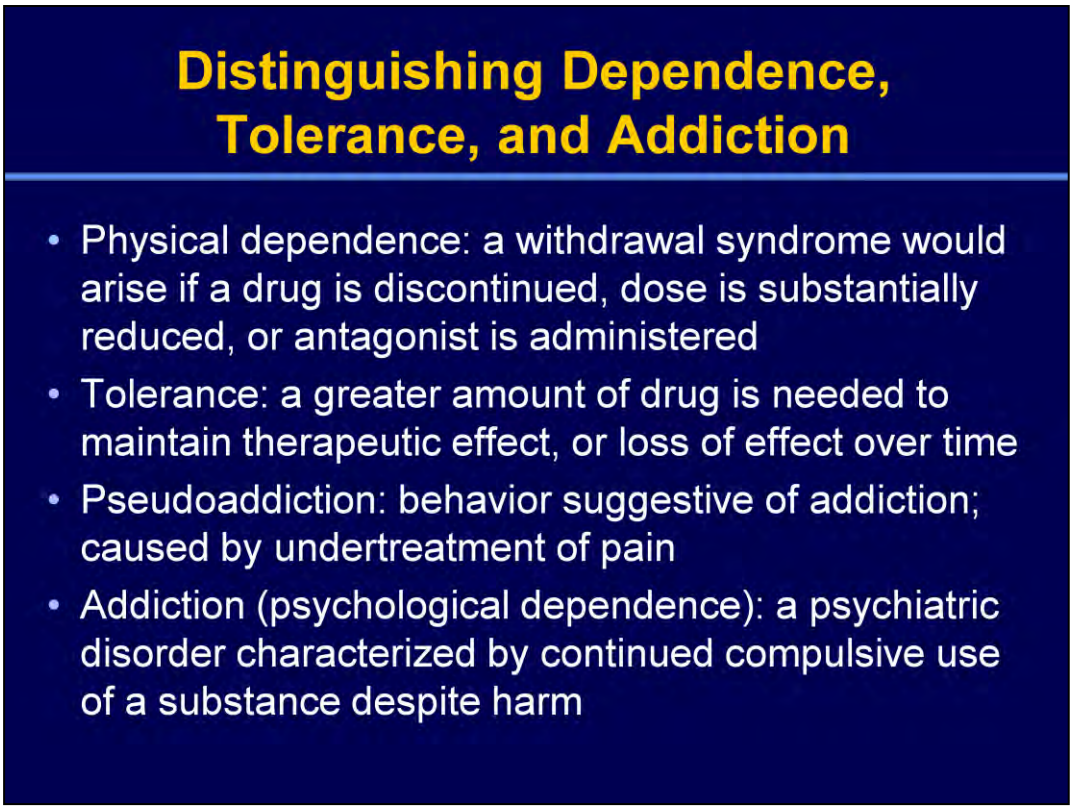
- This study evaluated the effectiveness of CR oxycodone in managing steady pain, brief (paroxysmal) pain, allodynia, and pain relief. Clinical effectiveness, disability, and patient treatment preference also were evaluated. The study's design is considered among the best because it assessed several types of pain.
- The study enrolled 50 patients with PHN of at least moderate intensity; 38 patients completed the trial. The patients were randomized to 10 mg of CR oxycodone or placebo every 12 hours, each for 4 weeks, using a double-blind crossover design. Pain intensity and pain relief were assessed daily, and steady and brief (paroxysmal) pain, allodynia, and pain relief were evaluated weekly.
- Compared with placebo, CR oxycodone produced significantly (*P*=0.0001) greater pain relief and reductions in steady pain, allodynia (*P*=0.0004), and paroxysmal spontaneous pain. CR oxycodone also achieved superior scores in global effectiveness, disability, and masked patient preference.
- Long-term effectiveness remains to be assessed.

Watson CPN, Babul N. Efficacy of oxycodone in neuropathic pain: a randomized trial in postherpetic neuralgia. *Neurology*. 1998;50:1837-1841.



- Tramadol has two known mechanisms of action: it is a weak μ-receptor agonist, and it blocks the reuptake of norepinephrine and serotonin. These properties suggest that it might be effective in patients with neuropathic pain.[1]
- A randomized, double-blind, placebo-controlled, crossover trial evaluated the efficacy of a slow-release formulation of tramadol in 45 patients with painful polyneuropathy.[2]
- Tramadol was started at a dose of 200 mg/day and was titrated to a maximum of 400 mg/day. Treatment periods were 4 weeks in duration for both tramadol and placebo.[2]
- Endpoints examined in the trial included spontaneous pain, paresthesia, and touch-evoked pain (allodynia). As shown on the slide, when treated with tramadol, patients had lower median ratings for spontaneous pain (P=0.001), paresthesia (P=0.001), and touch-evoked pain (P<0.001) than when they received a placebo.[2]
- The researchers concluded that tramadol relieves both continuing pain symptoms and allodynia in patients with painful polyneuropathy.[2]

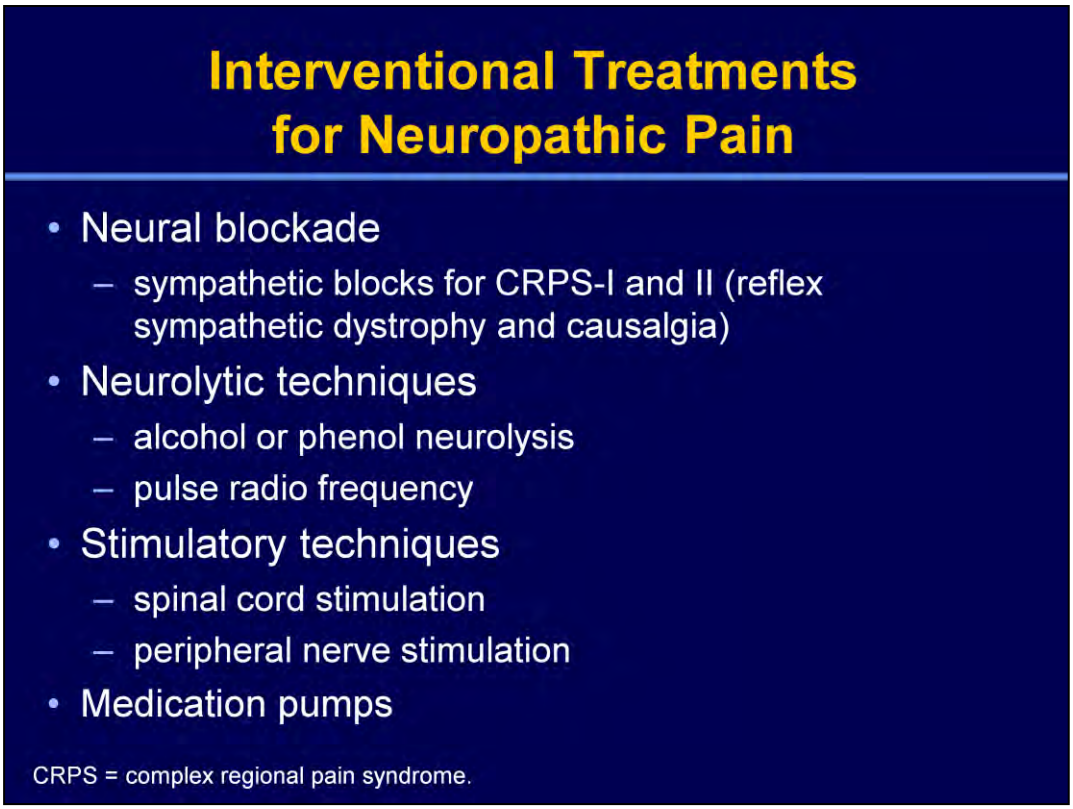
1. Harati Y, Gooch C, Swenson M, et al. Double-blind randomized trial of tramadol for the treatment of the pain of diabetic neuropathy. *Neurology*. 1998;50:1842-1846.
2. Sindrup SH, Andersen G, Madsen C, et al. Tramadol relieves pain and allodynia in polyneuropathy: a randomized, double-blind, controlled trial. *Pain*. 1999;83:85-90.



- This slide addresses the issue of aberrant drug-taking behaviors.
- Before considering initiation of opioid treatment, it is important for the physician, patient, and family to understand the distinction between physical dependence, tolerance, and addiction.
- Physical dependence is a pharmacologic effect characterized by the development of a withdrawal syndrome when an opioid drug is discontinued, when the dose is substantially reduced, or if an antagonist is administered. Dependence occurs in almost all patients on opioids, and does not connote addiction.[1]
- Tolerance means that a greater amount of drug is needed over time to maintain a therapeutic effect. The number of patients who develop clinically relevant tolerance is unknown. Tolerance may also occur to side effects, and thus may be beneficial. Some patients who develop tolerance can have their pain managed by judicious dose increases[2]; others who develop inexorable tolerance cannot have their pain managed by opioids. There is no evidence to support a role for analgesic tolerance in the development of drug addiction. Addiction is, however, often (though not always) associated with tolerance.
- Addiction is a psychiatric disorder consisting of continued, compulsive use of the substance despite harm.[1] *The Diagnostic and Statistical Manual of Mental Disorders* provides nine categories of opioid use or opioid-induced disorders, including diagnostic criteria for opioid dependence or opioid abuse.[3]
- True addiction (patient loss of control) may become obvious only when the physician stops prescribing the medicine. There is, however, little evidence that addiction is common within the chronic pain population. In a study reviewing the available data, it was found that prevalence estimates for addiction in patients with chronic pain ranged from 3% to 19%.[4]

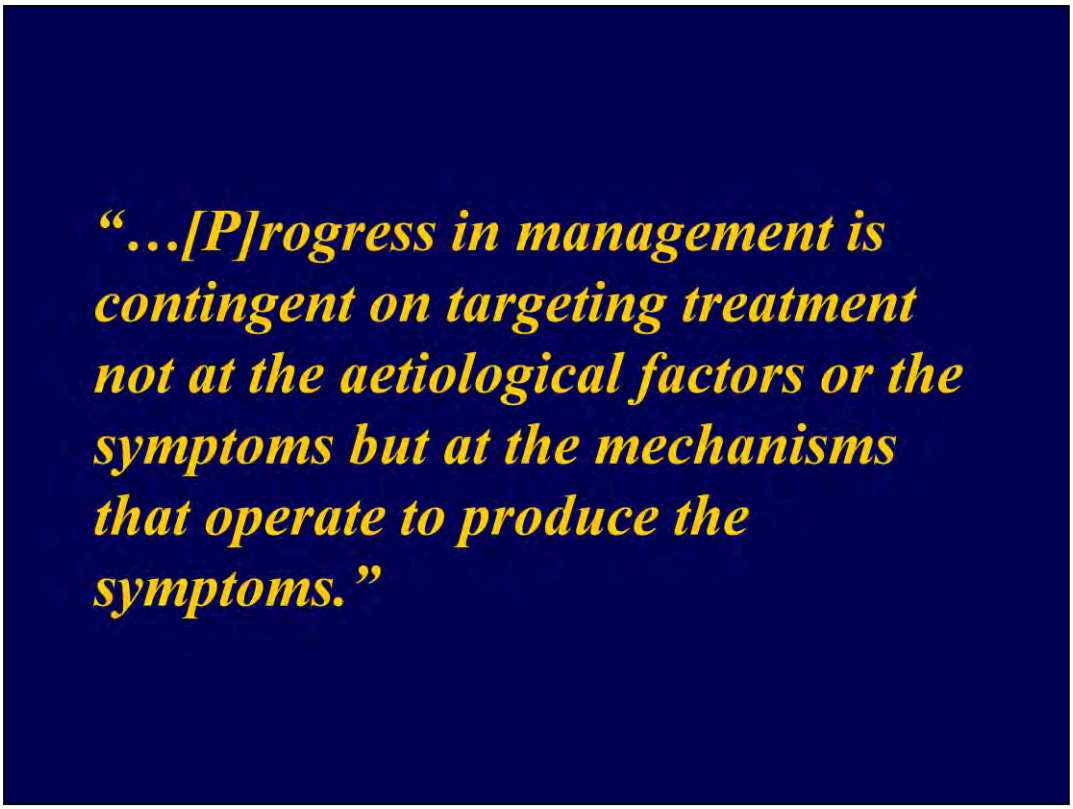
1. American Academy of Pain Medicine, American Pain Society, American Society of Addiction Medicine. *Definitions related to the use of opioids for the treatment of pain*. 2001. Available at: http://www.ampainsoc.org/advocacy/opioids2.htm. Accessed October 2, 2002.
2. Zenz M. Morphine myths: sedation, tolerance, addiction. *Postgrad Med J*. 1991;67:S100-S102.

3. American Psychiatric Association. *Diagnostic and Statistical Manual of Mental Disorders*. 4th Ed. Rev Ed. Washington, DC: American Psychiatric Publishing, Inc.; 2000:269-277.
4. Fishbain DA, Rosomoff HL, Rosomoff RS. Drug abuse, dependence, and addiction in chronic pain patients. *Clin J Pain*. 1992;8:77-85.



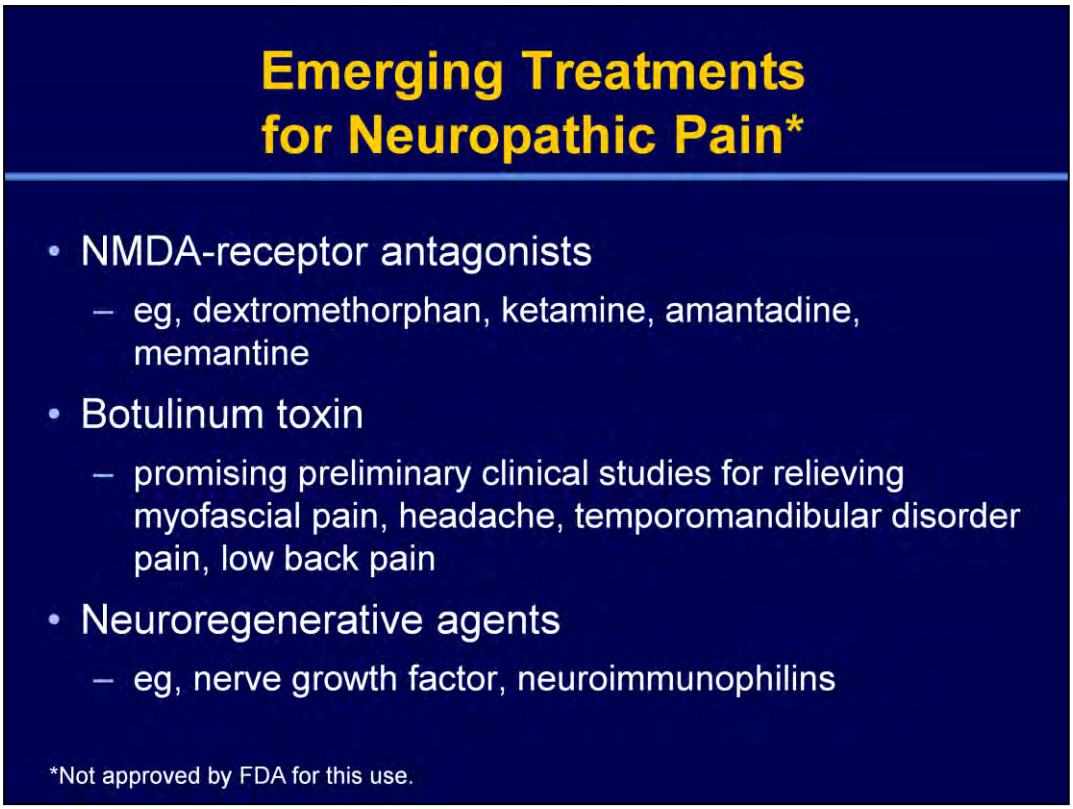
- Interventional treatments for neuropathic pain include neural blockade, neurolytic techniques, and stimulatory techniques.
- Neural blockade includes sympathetic blocks for complex regional pain syndrome type I (CRPS-I), which occurs without a definable nerve lesion and is also called reflex sympathetic dystrophy, and complex regional pain syndrome type II (CRPS-II), which occurs when a definable nerve lesion is present; both syndromes are also known as causalgia.[1,2]
- Neurolytic techniques are primarily employed for pain caused by cancer.[3]
- Pumps and stimulators are the main interventional techniques in routine clinical use.[2] Stimulatory techniques encompass spinal cord and peripheral nerve stimulation.[4] The main advantage of spinal cord stimulation is that it is a nonpharmacologic intervention that spares patients pharmacy visits, bills, and side effects.[5]
- Spinal analgesia is widely used for neuropathic pain but is a less conservative therapy than spinal cord stimulation. By acting directly on the spinal cord, spinal analgesia may provide improved pain control with fewer side effects than do systemic drugs.
- Among these techniques, only spinal analgesia has been shown to be effective in randomized controlled trials (and even this has been studied only short-term).[4]

1. Galer BS, Dworkin RH. *A Clinical Guide to Neuropathic Pain*. Minneapolis, Minn: McGraw-Hill Companies Inc; 2000:120,135.
2. MacFarlane BV, Wright A, O'Callaghan J, Benson HAE. Chronic neuropathic pain and its control by drugs. *Pharmacol Ther*. 1997;75:1-19.
3. Katz N. Neuropathic pain in cancer and AIDS. *Clin J Pain*. 2000;16(suppl 2):S41-S48.
4. Portenoy RK, Kanner RM, eds. *Pain Management: Theory and Practice*. Philadelphia, Pa: FA Davis Company; 1996:278,293-294,306-307.
5. Gonzales GR. Central pain: diagnosis and treatment strategies. *Neurology*. 1995;45(suppl 9):S11-S16.



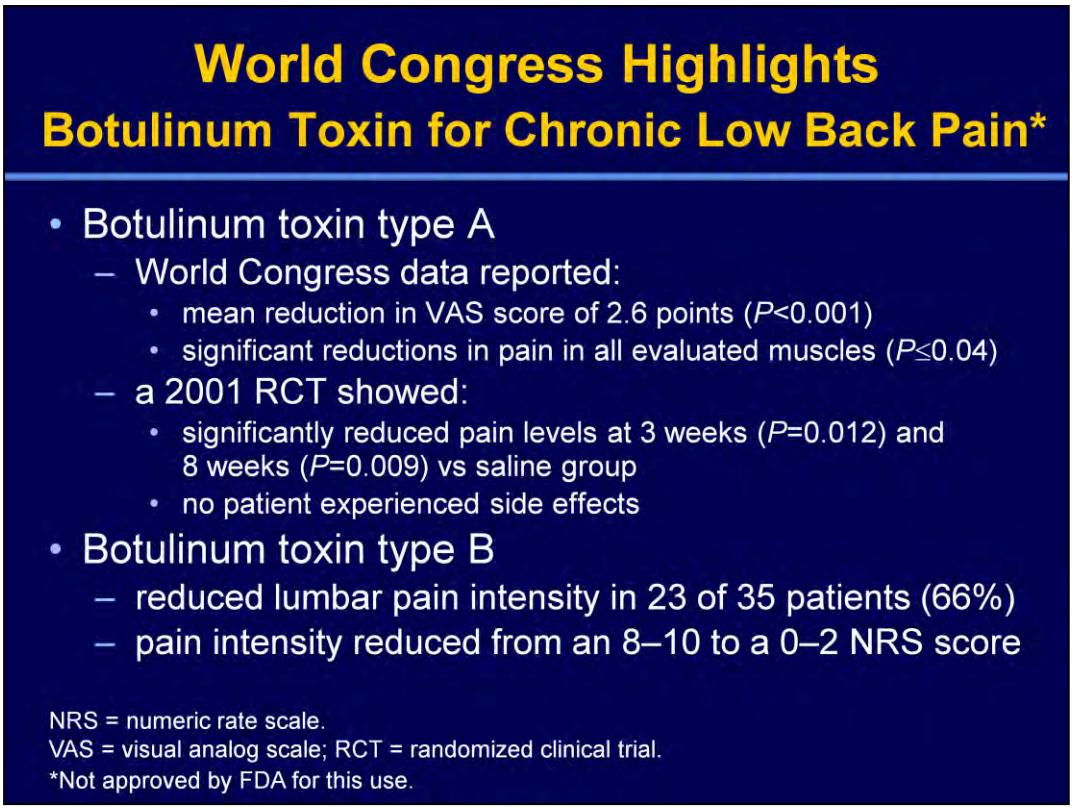
- There is a growing recognition that neuropathic pain disorders identified by disease, for example, PHN and painful diabetic neuropathy, most likely have multiple underlying pain mechanisms.
- Neuropathic pain syndromes, therefore, include heterogeneous groups of patients and differ in mechanisms, symptoms, treatment response, and prognosis.
- It follows that patients with different diseases may share more similarities in respect to the mechanisms of their pain than do other patients who have the same disease. For example, a patient with PHN may have pain mechanisms similar to those of a patient with painful diabetic neuropathy, but not similar to those of another patient with PHN.
- Rather than diagnosing patients based on disease, this perspective suggests that a major goal of pain assessment should be identifying the specific pathophysiologic mechanisms of pain. Once the mechanisms of pain are identified, the optimal treatment approach will be one that targets the specific mechanisms of each patient's pain.

Woolf CJ, Mannion RJ. Neuropathic pain: aetiology, symptoms, mechanisms, and management. *Lancet*. 1999;353:1959-1964.



- There are a number of potential new treatments for neuropathic pain in clinical trials—most focus on neurochemical changes that may be important in the induction and maintenance of neuronal hyperactivity and abnormal pain perception.
  - Recent clinical data suggest that chronic pain may result in the sensitization of the central nervous system, mediated in part by the excitatory amino acids, glutamate and aspartate. Inhibition of NMDA-receptor activation by NMDA antagonists such as dextromethorphan, ketamine, amantadine or memantine may act to potentiate the effects of existing analgesic therapies. For example, dextromethorphan has been shown to reduce morphine requirements in randomized controlled trials compared with morphine alone.[1,2] Whether this reduction is advantageous clinically, or whether it applies specially to neuropathic pain, is not yet clear and is the subject of continuing clinical studies.[3]
  - Botulinum toxin acts to block the release of acetylcholine at the neuromuscular junction, resulting in a temporary paralysis in injected muscle. The potent endopeptidase activity of clostridial neurotoxins, such as botulinum toxin type A, can be selectively retargeted to nociceptive afferent neurons, resulting in potent and sustained inhibition of neurotransmitter release. This has therapeutic potential for the treatment of chronic pain.[4-7]
  - Neurotrophic factors (ie, nerve growth factor) have been shown to be neuroprotective for damaged sensory neurons, providing a rationale for testing their effects in neuropathic pain states. Recent data have demonstrated potent analgesic effects of one factor (glial cell line–derived neurotrophic factor) in animal models of neuropathy, and implicated changes in sodium channels. The new findings provide a rational basis for the use of neurotrophic factors as a novel therapeutic treatment for neuropathic pain states. Neuroimmunophilins, such as cyclosporin A and FK506 (tacrolimus) also hold promise for treatment of neuropathic disorders, eg, diabetic neuropathy.[8,9]

1. Chevlen E. 2000; 2. Katz N. *J Pain Symptom Manage*. 2000;19:S37-S41; 3. Sang CN. 2000; 4. Gobel H et al. 2001; 5. Foster L et al. 2001; 6. Cheshire WP et al. 1994; 7. Freund B et al. 2000; 8. Boucher TJ et al. 2001; 9. Gold BG. 2000.



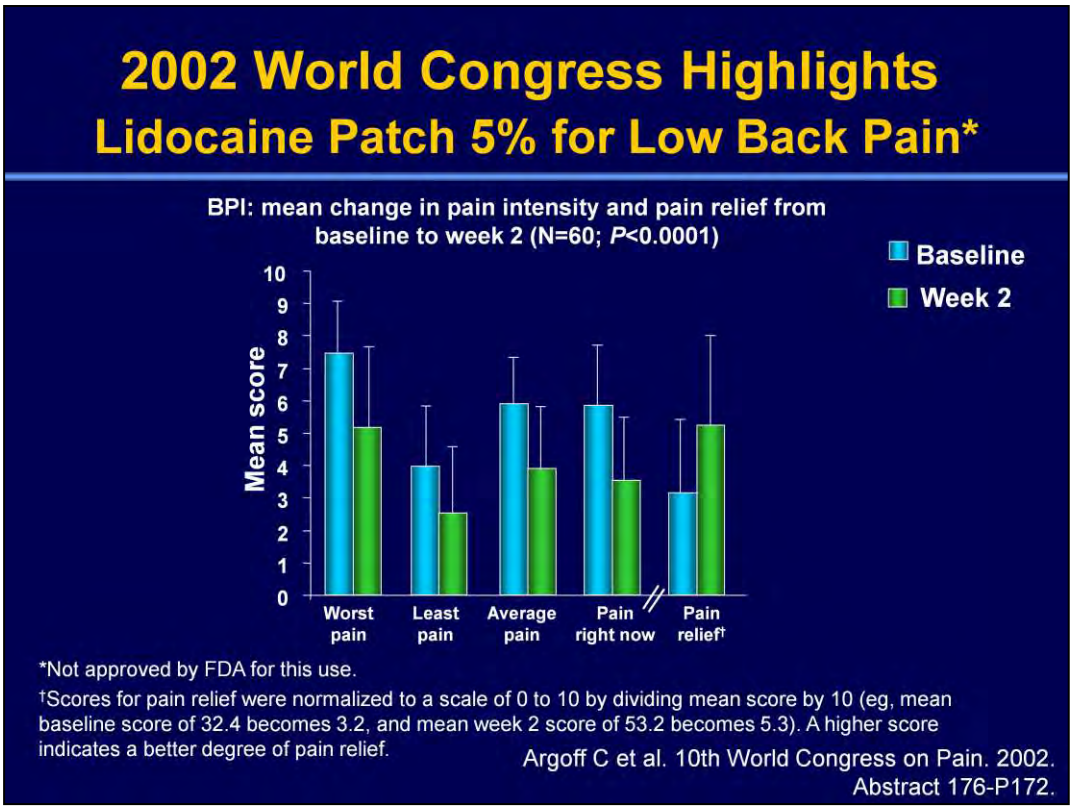
- At the August 2002 World Congress on pain, results from clinical investigations of many new treatment options, as well as data from clinical trials evaluating existing therapies for potentially broader clinical application, were presented. For example, investigational botulinum neurotoxins and targeted peripheral analgesics are being evaluated for chronic low back pain.[1]

- Safety and efficacy of botulinum toxin type A was evaluated in a retrospective, single-center review of patients with chronic low back pain. The primary outcome measure was reduction in pain as evaluated by change in visual analog scale (VAS) scores recorded prior to treatment and at each follow-up visit. Thirty-three patients with history of chronic low back pain received 50 botulinum toxin type A treatments (median dose 200 units). Overall, botulinum toxin type A provided a significant reduction in pain with a mean reduction of 2.6 points ($P<0.001$). Peak pain-relieving efficacy was observed at 22 to 60 days postinjection (mean reduction of 3.0 points, $P<0.001$). Significant reductions in pain were reported following injection in all evaluated muscles ($P\leq0.04$). Botulinum toxin type A was safe and well-tolerated with no adverse events reported, suggesting that it may provide safe and effective pain relief for patients with chronic low back pain.[2]

- Similarly, a recently published randomized, double-blind study compared the effects of 200 units of botulinum toxin type A and normal saline. At 3 weeks, degree of relief exceeded 50% (VAS score) in 11 of 15 patients (73.3%) in the treatment group compared with 4 of 16 (25%) in the saline group. At 8 weeks, 9 of 15 patients (60%) in the treatment group vs 2 of 16 (12.5%) in the saline group reported pain relief.[3]

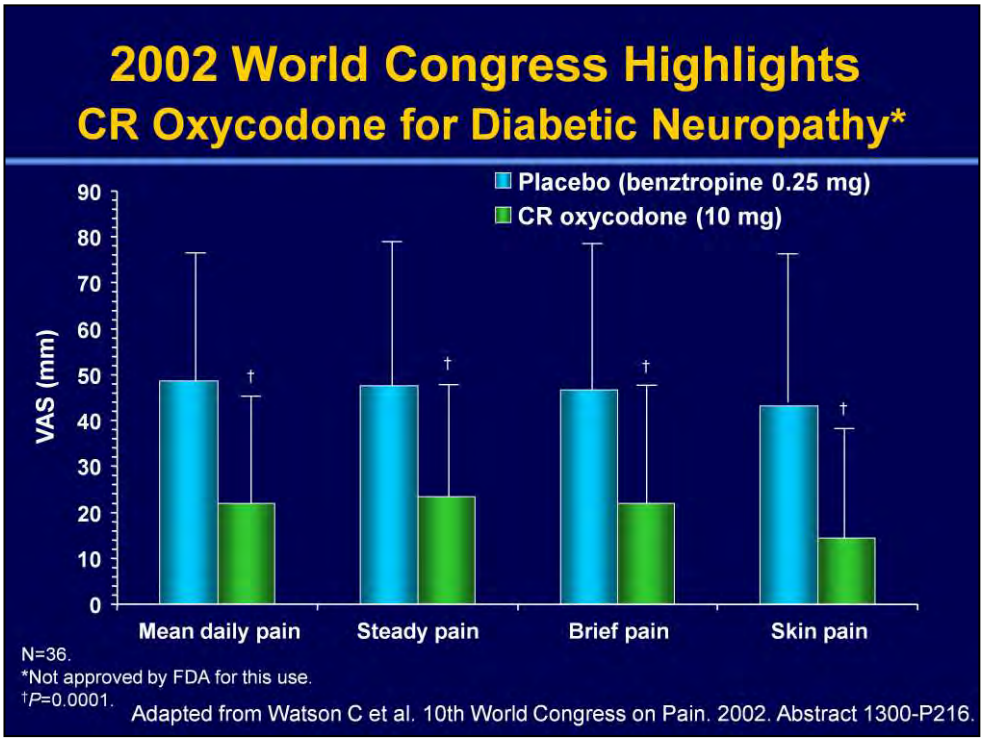
- Safety and efficacy of botulinum toxin type B was also evaluated in a prospective, open-label study of 35 patients with back pain for at least a 6-month period. The numeric rate scale (NRS; range 0–10) was used to rate the severity of symptoms. Patients with lumbar magnetic resonance images showed no evidence of surgical herniated disc. Prior to injection most patients reported 10 on the NRS; none were below 8. Patients were injected with 2 cc botulinum toxin type B (10,000 U) divided among the lumbar muscles. Sixty-six percent of the patients reported improvements in their lumbar pain intensity and severity, and in lumbar motion. Most patients were at 0 to 2 on the NRS postinjection. Adverse effects were minor and transient, consisting mainly of dry mouth (40%) and pain at the injection site. Findings suggest botulinum toxin type B is an effective agent for treatment of chronic low back pain.[1]

1. Opida CL. In: *Program and Abstracts of the IASP 10th World Congress on Pain.* 2002. Abstract 1341-P257.
2. Lang AM. In: *Program and Abstracts of the IASP 10th World Congress on Pain*. 2002. Abstract 1351-P267.
3. Foster L et al. *Neurology.* 2001;56:1290-1293.



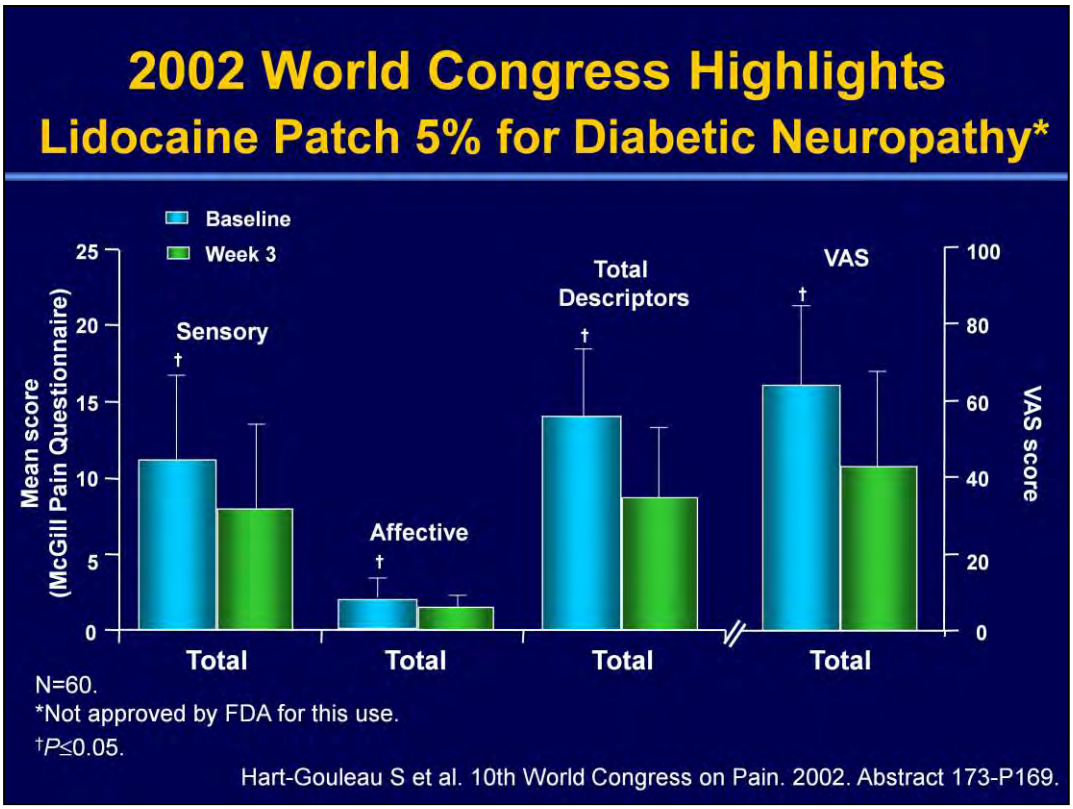
- The lidocaine patch 5%, a targeted peripheral analgesic that is currently FDA-approved for the treatment of PHN, was also evaluated for the treatment of chronic low back pain.
- The effectiveness of the lidocaine patch 5% was evaluated in both acute and chronic low back pain (LBP) after 2 weeks of daily treatment. Sixty patients participated in a prospective, multicenter, open-label pilot study. Patients were stratified into four groups (1: acute LBP—up to 6 wk; 2: subacute LBP—6 wk to 3 mo; 3: short-term chronic LBP—3 mo to 12 mo; 4: long-term chronic LBP—up to 1 yr), and up to four patches were applied daily (24 h/d) to the area of maximal pain intensity as add-on therapy to the patients' current regimen. Effectiveness was measured using the Brief Pain Inventory (BPI), Beck Depression Inventory, Patient/Investigator Global Assessment of Pain Relief, Patient/Investigator Global Satisfaction, and the Neuropathic Pain Scale (NPS).
- This figure shows the results of the BPI scores. The lidocaine patch 5% produced significant (*P*=<0.0001) reductions in pain intensity and pain interference with daily activities as measured by the BPI. The lidocaine patch 5% was safe and well tolerated with no serious or systemic adverse events or drug-drug interactions.

Argoff C, Nicholson B, Moskowitz M, Backonja M, Wheeler A, Gammaitoni A. Effectiveness of lidocaine patch 5% (Lidoderm®) in the treatment of low back pain (LBP). In: *Program and Abstracts of the IASP 10th World Congress on Pain*. August 17–22, 2002; San Diego, Calif. Abstract 176-P172.



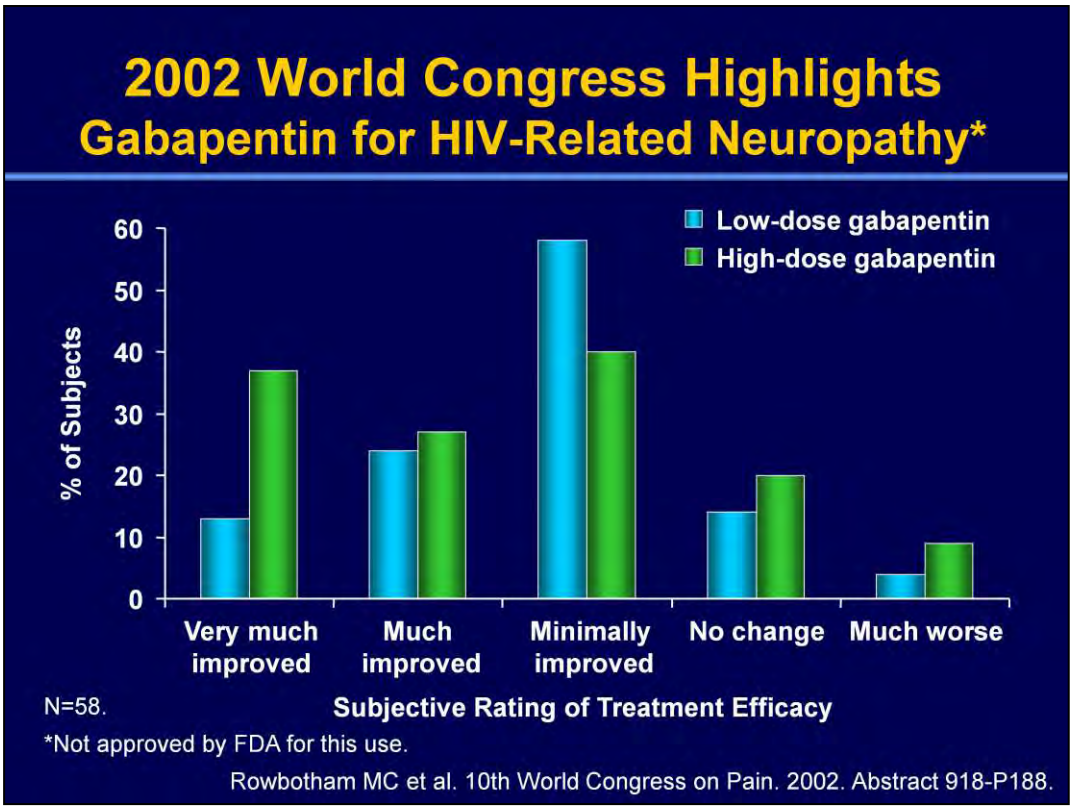
- Opioids and targeted peripheral analgesics are also being evaluated in patients with painful diabetic neuropathy. For example, the following studies presented at the August 2002 World Congress on Pain demonstrate the use of CR oxycodone and the lidocaine patch 5%.
- In this study, patients with diabetic neuropathy with moderate or greater pain for at least 3 months were evaluated for efficacy, safety, and QOL while receiving CR oxycodone (OxyContin®) or active placebo. Patients underwent washout from all opioids 2 to 7 days before randomization to 10 mg CR oxycodone or placebo (0.25 mg benztropine) q12h. The dose was increased, approximately weekly, to a maximum of 40 mg q12h CR oxycodone or 1 mg q12h benztropine, with crossover to the alternate treatment after a maximum of 4 weeks. Acetaminophen, 325 to 650 mg q4–6h prn was provided as rescue.
- Thirty-six patients were evaluable for efficacy (21 men, 15 women, mean age 63.0 ± 9.4 years). CR oxycodone resulted in significantly lower (*P*=0.0001) mean daily pain (21.8 ± 20.7 vs 48.6 ± 26.6 mm VAS), steady pain (23.5 ± 23.0 vs 47.6 ± 30.7 mm VAS), brief pain (21.8 ± 23.5 vs 46.7 ± 30.8 mm VAS), and skin pain (14.3 ± 20.4 vs 43.2 ± 31.3 mm VAS).
- SF-36 scores were significantly better with CR oxycodone for Physical Functioning (*P*=0.0029), Pain Index (*P*=0.0001), Vitality (*P*=0.0005), Social Functioning (*P*=0.0369), Mental Health Index (*P*=0.0317), Standardized Physical Component (*P*=0.0002), and Standardized Mental Component (*P*=0.0338).
- The total pain and disability score (16.8 ± 15.6 vs 25.2 ± 16.7; *P*=0.004) was lower for CR oxycodone.
- The results of this study suggest that CR oxycodone can be effective for the management of painful diabetic neuropathy.

Watson C, Moulin D, Watt-Watson J, et al. Controlled release oxycodone in painful diabetic neuropathy. In: *Program and Abstracts of the IASP 10th World Congress on Pain*. August 17–22, 2002; San Diego, Calif. Abstract 1300-P216.



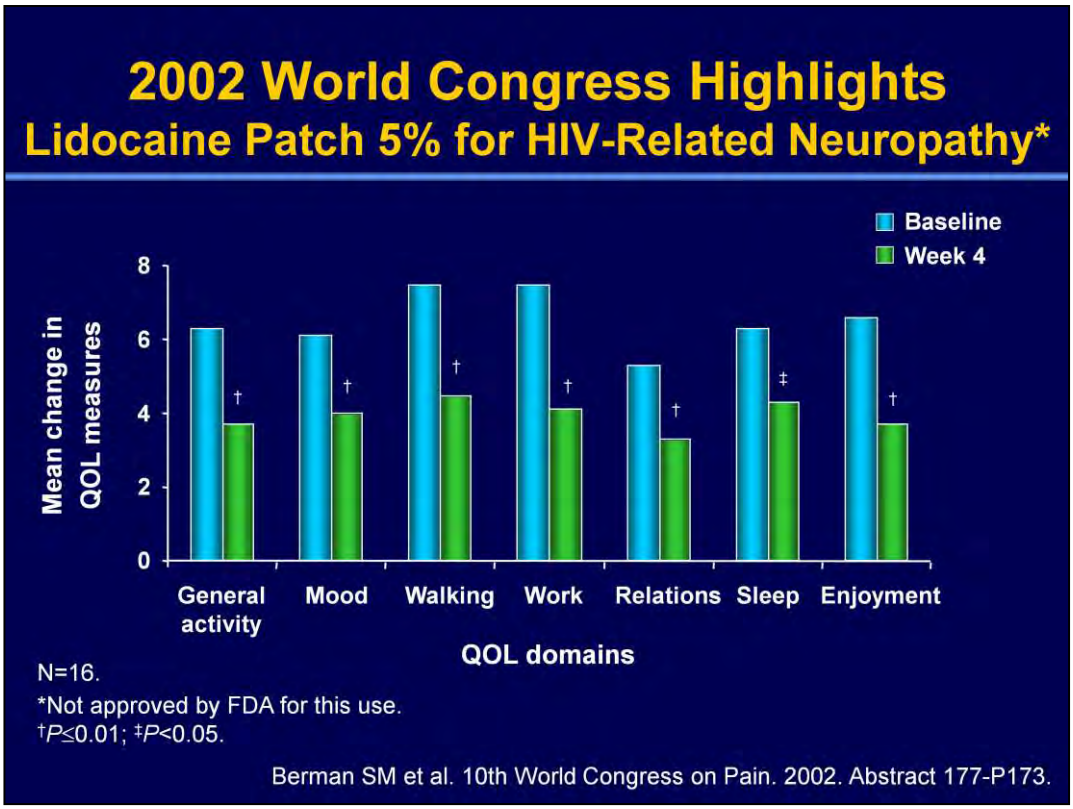
- The third set of studies assessed the safety, efficacy, and tolerability of lidocaine patch 5%, an FDA-approved treatment for PHN, for the treatment of painful diabetic neuropathy.[1]
- The effect of the lidocaine patch on distinct neuropathic pain qualities in patients with painful diabetic neuropathy (DN) was evaluated. Sixty patients were stratified into two groups (1: DN with allodynia; and 2: DN without allodynia) and received lidocaine patch 5% in an open-label fashion for a 3-week period. Up to four patches were applied daily (18 h/d) to the area of maximal pain intensity as add-on therapy to the patients' current regimen. Efficacy measures included BPI, McGill Pain Questionnaire, Beck Depression Inventory, Profile of Mood States, SF-36 and the NPS. Safety measures included monitoring lidocaine blood levels as well as adverse events. Composite NPS efficacy measures included the NPS-10 (a sum score of all 10 numerical items); NPS-8 (score of all 8 pain descriptors, excluding "unpleasantness" and "global intensity"); NPS-4 (score of the pain qualities thought not to be primarily related to peripheral dermal pathophysiologic events); and NPS-NA (score of all 8 nonallodynic items).[1]
- The lidocaine patch 5% produced positive improvements in pain intensity and pain relief of the most common pain qualities reported by patients with diabetic neuropathy, irrespective of the presence of allodynia. The lidocaine patch 5% was safe and well tolerated; the most common adverse events were skin-related (eg, burning sensation, photosensitivity)[1,2]
- Lidocaine patch 5% can be used for peripheral neuropathy; however, there may be issues with adhesion on moving extremities.

1. Hart-Gouleau S, Gammaitoni A, Galer B, Domingos J, Dworkin R. Open-label study of the effectiveness and safety of lidocaine patch 5% (lidoderm) in patients with painful diabetic neuropathy. In: *Program and Abstracts of the IASP 10th World Congress on Pain*. August 17–22, 2002; San Diego, Calif. Abstract 173-P169.
2. Gammaitoni AR, Galer BS, Dworkin R. Effectiveness of lidocaine patch 5% (lidoderm) on various pain qualities associated with diabetic neuropathy: a prospective trial using the neuropathic pain scale (nps). In: *Program and abstracts of the IASP 10th World Congress on Pain*. August 17–22, 2002; San Diego, Calif. Abstract 174-P170.



- Data from clinical trials that evaluated existing therapies for potentially broader applications were also presented at the August 2002 World Congress on Pain. For example, two treatments currently approved by the FDA for PHN, gabapentin and the lidocaine patch 5%, are being evaluated for the treatment of HIV-related neuropathy.
- In one study, adult HIV-positive patients with painful polyneuropathy were randomized to 4 weeks of therapy with either low-dose (900 mg/d) or high-dose (3,600 mg/d) gabapentin in a double-blind, multicenter trial. Evaluations included daily diary pain and sleep ratings, SF-MPQ, POMS, SF-36 Quality of Life, Multidimensional Pain Inventory, and Global Impression of Change ratings. Fifty-eight subjects completed the 4-week trial.
- In this study, pain declined by 30% with low-dose gabapentin and by 46% with high-dose gabapentin (P=0.04). High-dose gabapentin provided superior pain reduction in subjects who completed the trial; however, more subjects on the high dose discontinued the study because of adverse events. Gabapentin has an acceptable side-effect profile and minimal drug-drug interactions, features especially important for HIV-infected individuals utilizing complex antiretroviral treatment regimens.

Rowbotham MC, Young S, Sacks G, et al. Gabapentin for painful HIV neuropathy: blinded, randomized trial comparing high and low doses. In: *Program and Abstracts of the IASP 10th World Congress on Pain*. August 17–22, 2002; San Diego, Calif. Abstract 918-P188.



- The lidocaine patch 5%, a targeted peripheral analgesic that is currently FDA-approved for the treatment of PHN, was also evaluated for the treatment of HIV-related neuropathy.
- The effectiveness of lidocaine patch 5% in reducing pain interference with QOL in HIV-associated painful peripheral neuropathy was evaluated in a prospective, multiple-dose, open-label pilot study as add-on to existing therapy. BPI scores assessed pain interference with QOL.
- Eight patients completed 4 weeks of treatment with significant improvement in QOL ($P<0.05$). No systemic side effects were observed, nor were drug interactions. The results suggest that the lidocaine patch may be a safe and effective option for HIV-associated neuropathic pain.

Berman SM, Justis JC, Ho M, Butt AA, Risa K, Gammaitoni A. Lidocaine patch 5% (lidoderm) significantly improves quality of life (qol) in hiv-associated painful peripheral neuropathy. In: *Program and Abstracts of the IASP 10th World Congress on Pain*. August 17–22, 2002; San Diego, Calif. Abstract 177-P173.

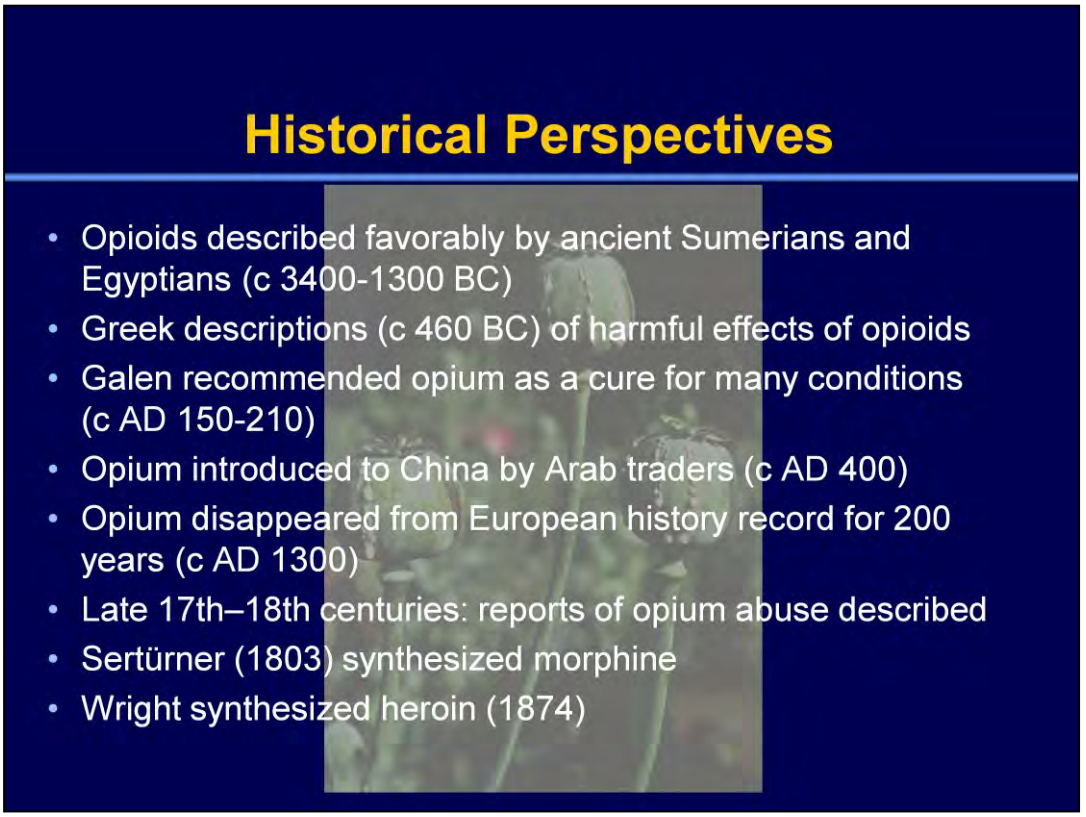
- Most patients can obtain clinically meaningful relief with appropriate treatment.
- Given the multiple mechanisms of neuropathic pain, polypharmacy may be required for patients who do not respond adequately to treatment with a single agent.
- Drugs should be titrated aggressively either to the point where significant pain relief is achieved or intolerable side effects occur.
- New treatments for neuropathic pain that target specific pathways may help address the underlying mechanisms involved in pain.
- Treatment should balance efficacy, safety, and tolerability, and progress from the least to the most invasive treatments. More invasive treatments are not necessarily more effective than less invasive ones. The goals of treatment should include not only reducing pain as much as possible but also improving the patient's QOL.[1]
- Patients with inadequate pain relief may benefit from referral to multidisciplinary pain treatment centers.[2]

1. Galer BS, Dworkin RH. *A Clinical Guide to Neuropathic Pain.* Minneapolis, Minn: The McGraw-Hill Companies, Inc; 2000:53-55.
2. Cunningham AL, Dworkin RH. The management of post-herpetic neuralgia. *BMJ*. 2000;321:778-779.

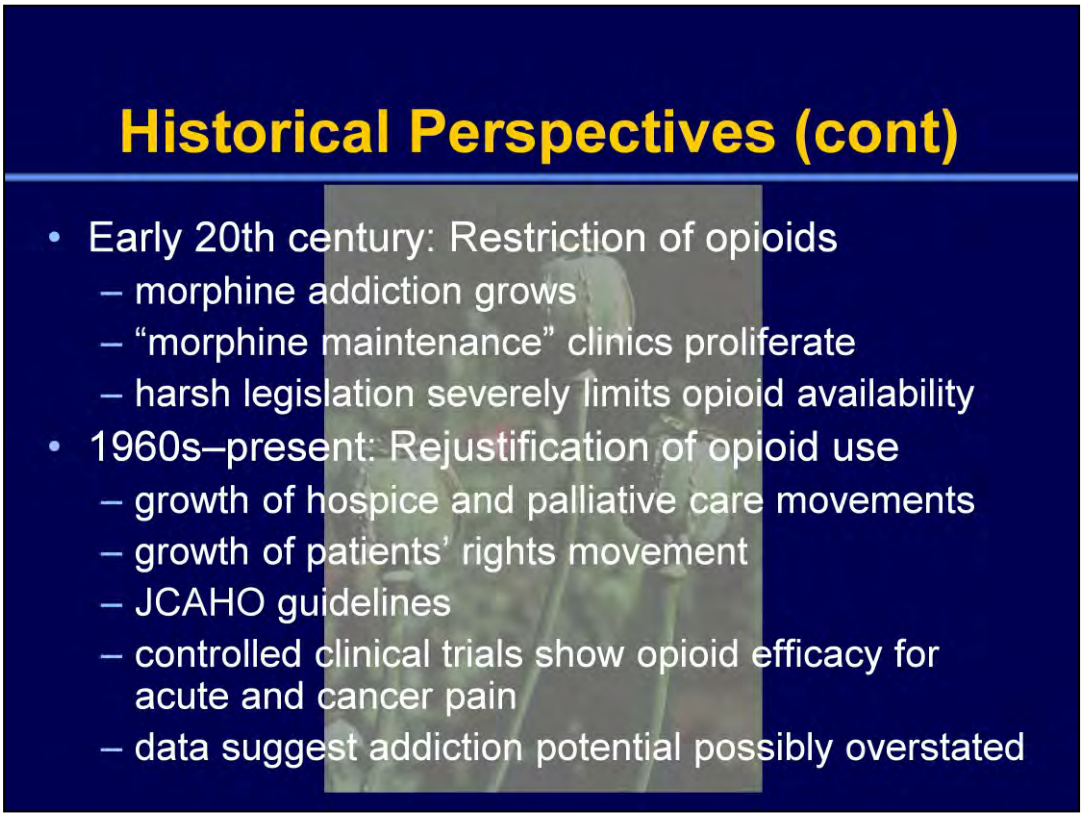
Rational Polypharmacy for Neuropathic Pain Disorders

Numerous therapies have been tried. Many have been without effect. Some have brought some relief but pain scores remain high and the pain remains debilitating for this patient.


THOMSON
PROFESSIONAL
POSTGRADUATE SERVICES
Advances in Opioid Analgesia:
Maximizing Benefit, Minimizing Harm
Michael H. Moskowitz, MD, MPH
Bay Area Pain Medical Associates

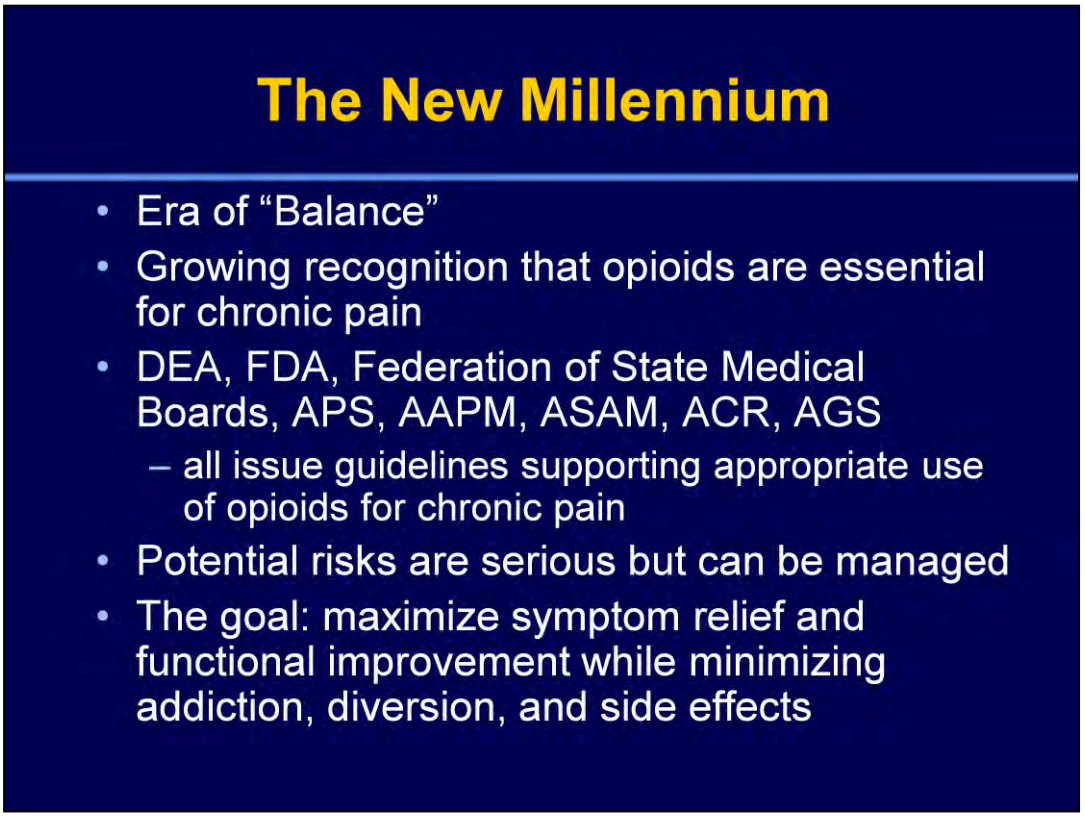


- Opioids have a long history of use and abuse throughout human civilization, with perspectives oscillating between recognition of their medical importance in pain relief and concerns about their addictive power.
- In ancient civilizations, opioids were described favorably by Sumerians and Egyptians.
- However, by the fifth century BC, Greeks were writing about the harmful effects of opioids, including addiction, and Diagoras of Melos wrote that “it is better to suffer pain than to become dependent upon opium.” At the same time (~300 BC), Alexander the great introduced opium to Persia and India.
- In the second century AD, the Roman physician and philosopher Galen recommended opium as a cure for many conditions. Opium was first introduced to China by Arab traders ~AD 400.
- By AD 1300, opium had fallen into disfavor throughout Europe. Opium was reintroduced in Europe during the Reformation (~AD 1500) and prescribed as a painkiller.
- In the late 17th and the 18th century, reports of opium abuse were described. However, growing of opium was encouraged in India, and opium was widely imported to China.
- In 1803, Sertürner synthesized morphine, and within decades it was widely employed medicinally.
- China’s attempt to suppress the cultivation and trade of opium peaked in the 1800s leading to the Opium Wars and ultimately the legalization of opium importation in China.
- Morphine addiction became a large problem during the American Civil War (1861-65).
- In 1874, Wright first synthesized heroin; in 1885 Dreser, working for The Bayer Company, developed process for the commercial production of heroin.



- In the early 20th century, as morphine addiction continued to rise, "morphine maintenance" clinics proliferated, and harsh legislation was enacted to severely limit opioid availability. Heroin use as a morphine step-down agent increases.
- However, in the 1960s through the present, the growth of the hospice, palliative care, and the patients' rights movements again focused attention on the medical importance of opioids for adequate pain relief. Controlled clinical trials demonstrated the efficacy of opioids for both acute and cancer pain and in 1999 the Joint Commission on Accreditation of Healthcare Organizations (JCAHO) approved standards that specifically mandated the rights of patients to receive appropriate pain management.
- An additional factor in favor of opioid treatment for pain relief, data suggested that addiction potential was possibly overstated.[1,2]

1. Porter J, Jick H. Addiction rare in patients treated with narcotics. *N Engl J Med*. 1980. Jan 10;302(2):123.
2. Perry S, Heidrich G. Management of pain during debridement: a survey of U.S. burn units. *Pain*. 1982;13:267-280.



- Medicine has now entered the new millennium, an era of "balance," in which numerous government and healthcare organizations have issued guidelines supporting the appropriate use of opioids for chronic pain.
- There is a growing recognition that opioid analgesics are essential treatment options for chronic pain, yet they do have serious risk potential, and these risks can be managed.
- The goal of physicians, then, is to maximize symptom relief and functional improvement while minimizing the risks and occurrence of addiction, diversion, and other complications.

Drug Enforcement Administration (DEA): www.usdoj.gov/dea/

US Food and Drug Administration (FDA): www.fda.gov/

Federation of State Medical Boards (FSMB): www.fsmb.org/

American Pain Society (APS): www.ampainsoc.org/

American Association of Pain Medicine (AAPM): www.painmed.org/

American Society of Pain Management (AAPM): www.aapainmanage.org/

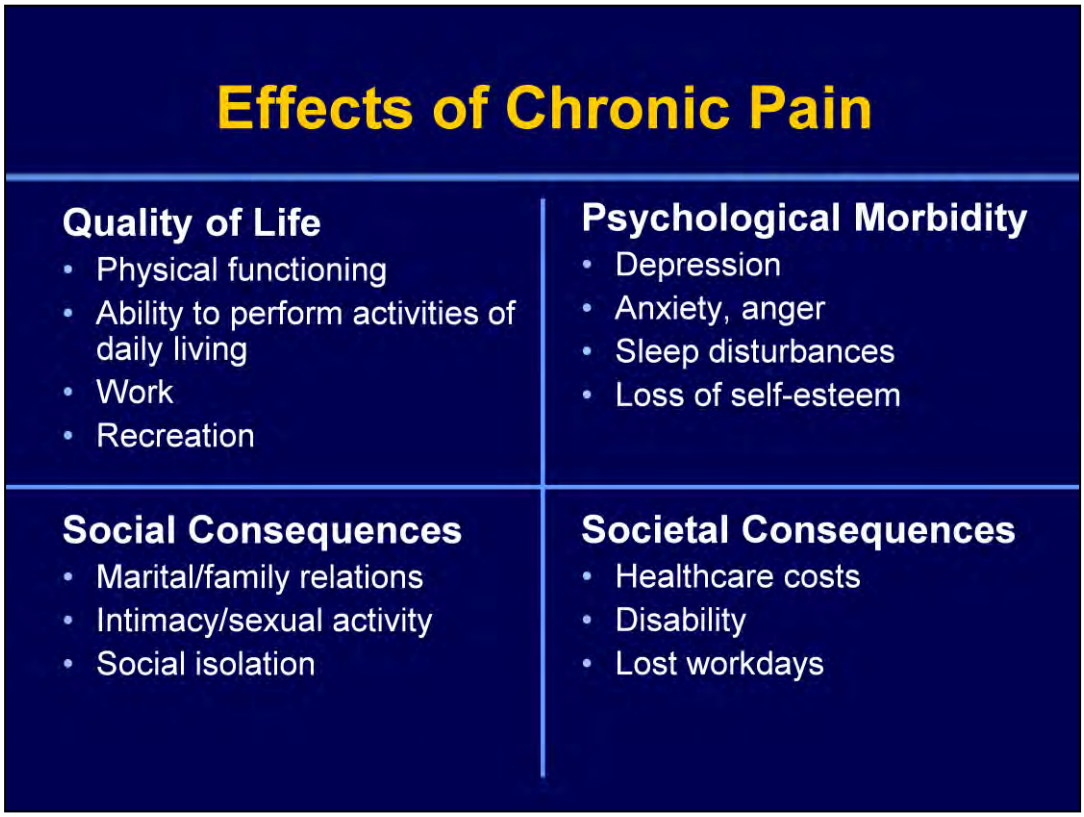
American Society of Addiction Medicine (ASAM): www.asam.org/

American College of Radiology (ACR): www.acr.org

American Geriatrics Society (AGS): www.americangeriatrics.org/

- Because of the inherent subjective nature of pain and the fact that the word "pain" itself connotes multiple meanings, the International Association for the Study of Pain (IASP) has established a standardized definition of pain.
- The definition makes several important points:
  - Pain is an unpleasant emotional experience as well as an unpleasant sensory experience. This distinction between the sensory aspects of pain and its emotional (or affective) component has had a great influence on both research on and the treatment of chronic pain.
  - Also emphasized by the IASP in defining pain is that pain is always subjective. If patients regard their experience as pain and if they report it in the same ways as pain caused by tissue damage, it should be accepted as pain.

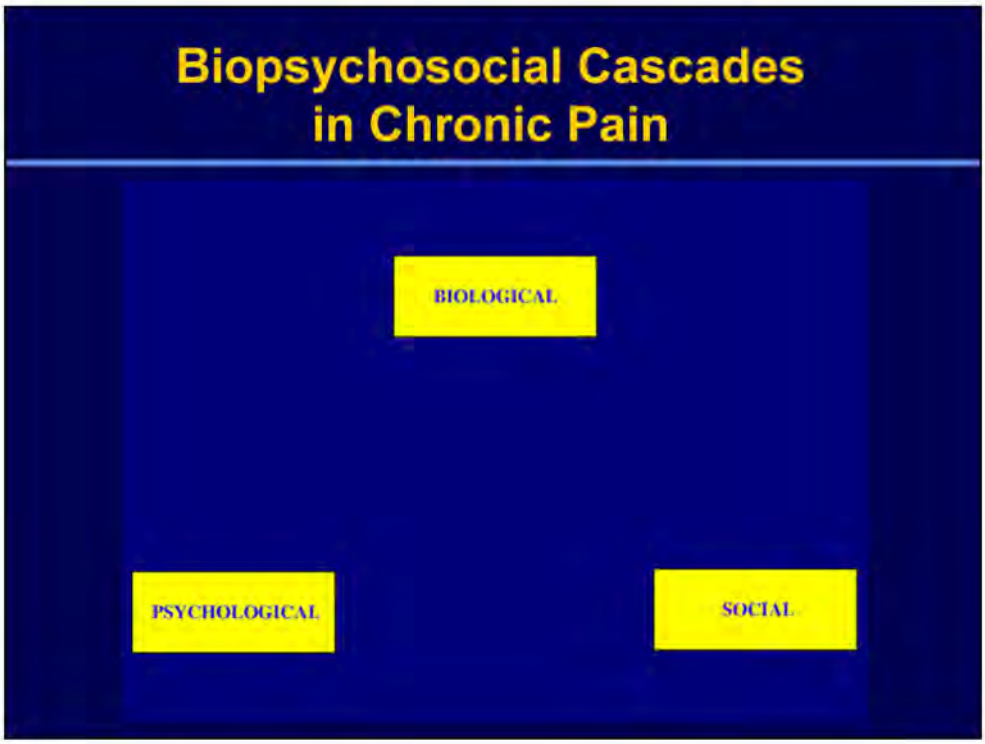
IASP Task Force on Taxonomy. In: Merskey H, Bogduk N, eds. *Classification of Chronic Pain*. 2nd ed. Seattle, Wash: IASP Press; 1994:209-214.



- Chronic pain has a wide range of negative effects, not only for the individual patient but for families and society as well.
- Both physical and psychological aspects of a patient's life may be impacted, including the ability to work or perform activities of daily living, sleep patterns, emotional state (depression, anxiety, anger), and self-esteem.
- Social, familial, marital, and/or sexual relations may be impaired, and patients may become socially isolated as they are no longer able to participate in their usual activities.
- The disability and lost workdays associated with chronic pain impose significant direct as well as indirect healthcare costs for society as a whole. The economic impact of chronic pain is staggering. Back pain, migraines, and arthritis alone account for medical costs of $40 billion annually; the total annual cost of pain from all causes is estimated to be more than $100 billion. Pain is the cause of 25% of all sick days taken yearly.[1]
- A growing scientific understanding of pain mechanisms has led to the evolving concept of pain as a disease state in its own right, one that may require ongoing treatment.
- However, do not expect analgesics to solve all these problems. A number of studies suggest that the best success in pain management relies on a multidisciplinary approach that includes patient education, medications, physical medicine, and psychological counseling. For example, when Becker et al compared the effect of multidisciplinary pain treatment (MPT) with that of treatment by a general practitioner after initial supervision by a pain specialist (GP group) in 189 patients with chronic, nonmalignant pain, they found that, after 6 months, the MPT group reported a statistically significant reduction in pain intensity (visual analogue scale score, $P<0.001$), improvement in psychological well-being (PGWB, $P<0.001$), quality of sleep ($P<0.05$), and physical functioning (Short Form 36–Physical Functioning, $P<0.05$) compared with the GP group.[2]

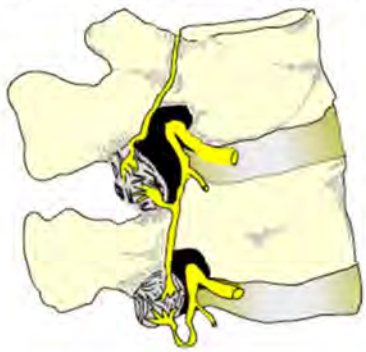
- Thus, a coordinated approach to pain management often provides the most efficient and cost-effective approach, which leads to patient empowerment (improved perception of personal control over pain) and the best clinical outcome.

1. *U.S. News & World Report*. Washington, DC: U.S. News & World Report L.P.; March 17, 1997:55-57, 60-62, 65, 67.
2. Becker N, Sjogren P, Bech P, Olsen AK, Eriksen J. Treatment outcome of chronic non-malignant pain patients managed in a Danish multidisciplinary pain centre compared to general practice: a randomized controlled trial. *Pain*. 2000;84:203-211.

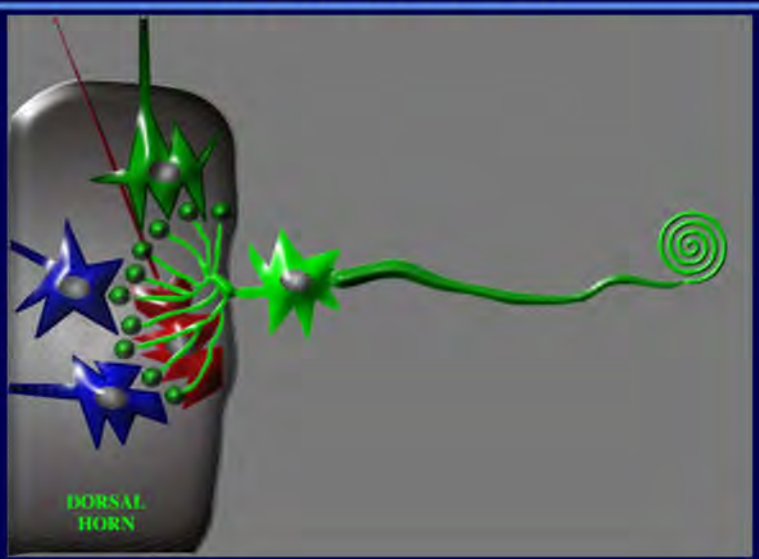

Biopsychosocial Cascades
in Chronic Pain
BIOLOGICAL
PSYCHOLOGICAL
SOCIAL

Chronic Inflammatory and Neuropathic Pain

Lumbar Degenerative Disc Disease with Facet Hypertrophy and Osteophyte Formation



Peripheral and Central Mechanisms of Chronic Pain



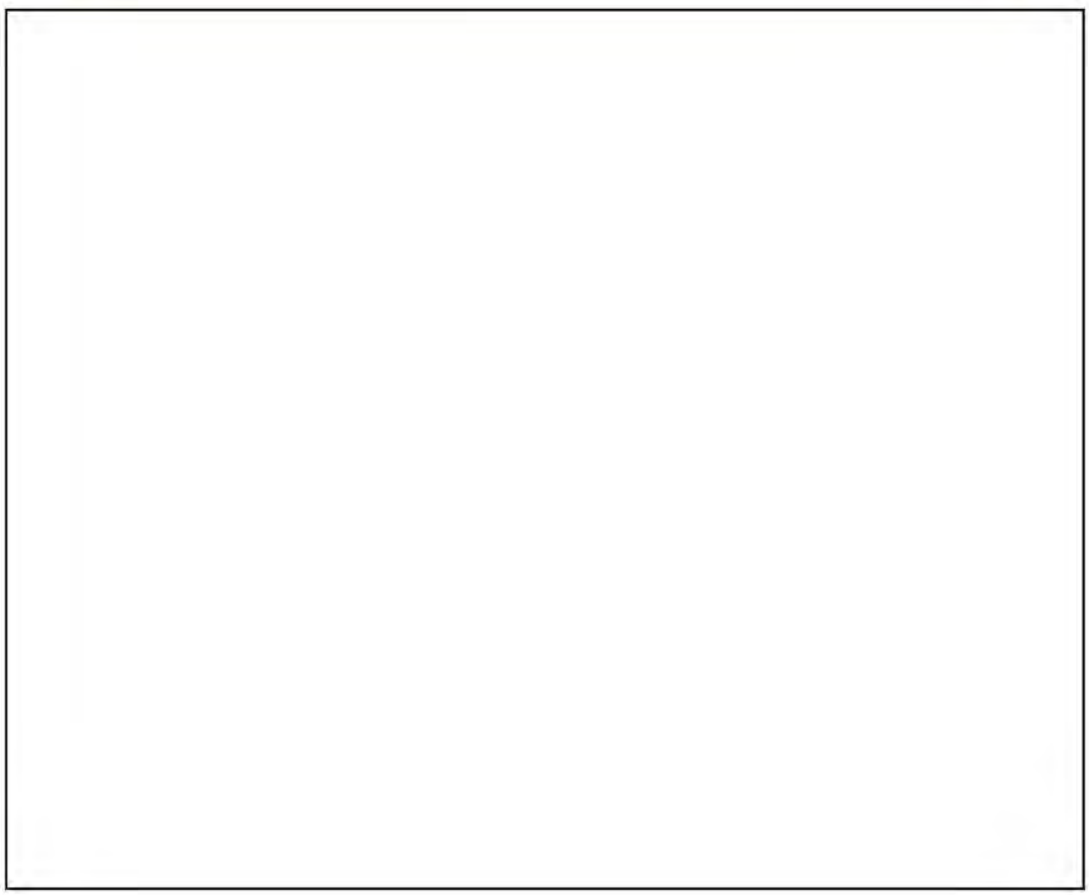
Pathophysiology of Neuropathic Pain: Peripheral Mechanisms

- Lactic acidosis in chronic spasm
- Chronic nerve inflammation—CGRP, SP, ATP
- Chemical excitation of non-nociceptors
- Recruitment of nerves outside of site of injury
- Increased sodium channel activity
- Increased sensitivity to sympathetic chemistry
- Ectopic discharge

Baron R. *Clin J Pain*. 2000;16:S12-S20.

Peripheral Processes in Chronic Pain

- Chemical and structural changes occur at the peripheral lesion. These include:
  - inflammatory changes
  - neuropathic changes
- Unchecked, these may lead to changes in the Central Nervous System.



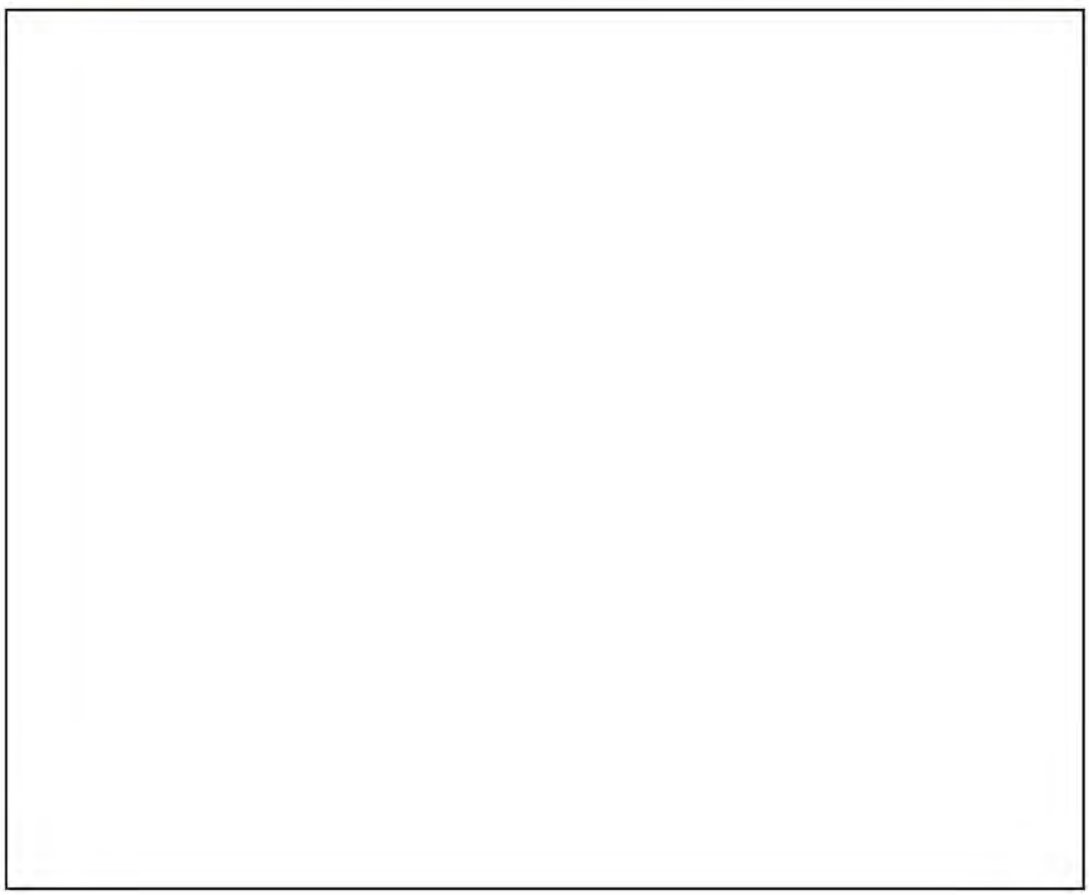
Pathophysiology of Chronic Pain: Central Mechanisms

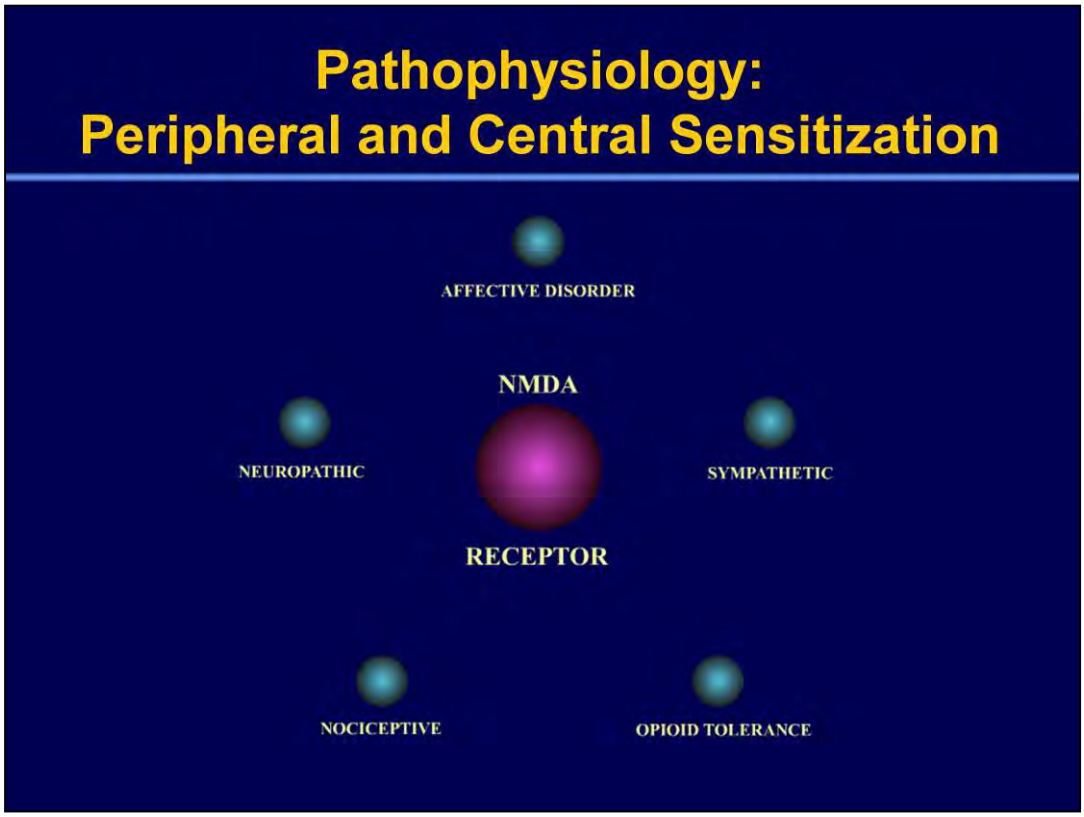
- Excitotoxicity
- Deafferentation
- Central sensitization—maintained by peripheral input
- Loss of GABAergic restraint
- Sympathetic involvement
- Antidromic neurogenic inflammation
- Central Nervous System inflammation
- Derangement of Hypothalamic-Pituitary-Adrenal Axis

Brookoff D. *Hosp Pract*. 2000:45-59.

Portenoy RK, Kanner RM, eds. *Pain Management: Theory and Practice*. FA Davis; 1996.

Roberts E. Adventures with GABA. *GABA in the Nervous System*. Lippincott, Williams and Wilkins; 2000.





Instructions to presenter: *The first thing to understand about this animation is that all roads lead back to the initial screen. It can be used to point out that all of these processes have a common pathway through the NMDA receptor and go no further. All animations have stop action and further buttons that lead to the next steps. To make the animation live, click anywhere on the screen. Move the cursor over a button and a pointing finger will appear and the button will change color. Lecture notes below only pertain to the nociceptive and neuropathic buttons since they are the most pertinent to this presentation.*

- As shown on the slides to follow, either continuous bombardment of the nervous system with nociceptive signals or peripheral or central nervous system injury can cause changes in the nervous system that may become persistent and irreversible.
- **Neuropathic Button:** First we see the C and A-Beta fibers in the dorsal horn. ***(click)*** Next, damage to the nerve before the DRG. ***(click)*** Here we see the ingrowth of A-Beta fibers following nerve injury to pain signal transmitting superficial lamina of the dorsal horn, resulting in the clinical manifestation of allodynia. ***(click)*** Here is a similar molecular view as the previous slide, resulting in wind-up.
- **Nociceptive Button:** Following injury and inflammation, nociceptors may become “sensitized,” resulting in decreased thresholds for activation and spontaneous discharge. Here we see a process of inflammation changing from acute to chronic and then focusing down to the microscopic and molecular level of windup. ***[Click]*** Next, a posterior view of a lumbar motion segment with Z joints (facet joints). ***[Click]*** The joint becomes inflamed. ***[Click]*** Here is a microscopic look into the zone of inflammation and the release of inflammatory chemicals activating the nociceptors. ***[Click]*** The nociceptors release substance-P, adenosine triphosphate and calcitonin gene-related peptide that activates nonnociceptors resulting in the transmission of signals that produce a perception of pain. ***[Click]*** This all connects to the central nervous system and produces windup. ***[Click]*** This shows the molecular view of windup pain. Initially a non–pain-

producing signal causes the release of glutamate to non-NMDA receptors and no pain. ***[Click]*** Prolonged firing of c-fibers causes the release of glutamate, which acts on NMDA receptors in the spinal cord. ***[Click]*** Substance-P is released and depolarization is amplified, resulting in a signal interpreted as pain. ***[Click]*** Here, NMDA receptors are blocked by magnesium; however, with the pairing of substance-P and glutamate over time, the block is released ***[Click]***. ***[Click]*** Glutamate attaches and shows wind-up on the postsynaptic action potential.

What Types of Pain Syndromes May Respond to Opioids?

- Categories
  - acute pain
  - cancer pain
  - chronic (persistent) noncancer pain
- Temporal pattern
  - episodic/continuous
- Mechanisms
  - nociceptive (somatic or visceral)
  - neuropathic (peripheral or central)

- Although there are common misperceptions that opioids are effective only for certain types of pain, or should be used only in the short term (for acute pain) or for cancer pain, the reality is that in the absence of effective alternatives, opioids are an indispensable tool for treating a wide range of pain types.[1-4]
- In addition to short-term use, opioids can be safely used long term (for cancer or chronic, persistent noncancer pain) either as needed for episodic pain or regularly for continuous pain, with appropriate monitoring, attention to management of side effects, and careful selection of agent and dosing schedule.
- Opioid analgesics may be used to treat both nociceptive pain as well as pain of neuropathic origin.[5]

1. Dellemijn PL. Opioids in non-cancer pain: a life-time sentence? *Eur J Pain*. 2001;5:333-339.
2. Schofferman J. Long-term opioid analgesic therapy for severe refractory lumbar spine pain. *Clin J Pain*. 1999;15:136-140.
3. Rowbotham MC, Reisner-Keller LA, Fields HL. Both intravenous lidocaine and morphine reduce the pain of postherpetic neuralgia. *Neurology*. 1991;41:1024-1028.
4. Lipman AG. Treatment of chronic pain in osteoarthritis: do opioids have a clinical role? *Curr Rheumatol Rep*. 2001;3:513-519.
5. Portenoy RK. Opioid analgesics. In: Portenoy RK, Kanner RM, eds. *Pain Management*: Theory and Practice. Philadelphia, Pa: FA Davis Company; 1996:248-276.

- While the remainder of this module will focus on chronic pain, it is important to note that acute postoperative pain is poorly controlled.
- In a landmark study published in the *Annals of Internal Medicine* in 1973, Marks and Sachar reported that 73% of patients with severe acute pain continued to experience pain despite treatment. Twenty-two years later, in 1995, Warfield and Kahn published results in *Anesthesiology* that were distressingly similar: 77% of adults reported pain after surgery, with 71% continuing to experience pain even after receiving pain medication.[1,2]
- Because pain is dynamic, unrelieved acute pain may lead to progressively increasing pathophysiology in the nervous system, which may result in significant morbidity and, in certain populations, even mortality.
- Additional benefits of aggressive pain prevention and control include
  - Shortened hospitalization and recovery periods
  - Reduced postoperative analgesic requirements with aggressive preoperative and intraoperative management
  - Reduced risk of progression to chronic pain
  - Decreased patient discomfort
  - Increased patient satisfaction
  - Reduced healthcare costs

1. Marks RM, Sachar EJ. Undertreatment of medical inpatients with narcotic analgesics. *Ann Intern Med*. 1973;78:173-181.

2. Warfield CA, Kahn CH. Acute pain management. Programs in US hospitals and experiences and attitudes among US adults. *Anesthesiology*. 1995;83:1090-1094.

- Pharmacologic therapy is most effective when combined with nonpharmacologic strategies to optimize pain management (eg, education or exercise programs, cognitive-behavioral therapy, heat, cold, massage, relaxation).
- Because the underlying cause of chronic pain may not be known or fully treatable, it is useful to think about pain itself as the disease. When not aggressively treated, pain can become a source of serious morbidity, analogous to untreated hyperglycemia in patients with diabetes, and may also significantly degrade functionality and quality of life.
- Opioids are an important class of therapeutic agents used to manage chronic pain. Fast-onset, short-acting opioids should be prescribed only on an “as-needed” basis for breakthrough or incident pain. Long-acting, sustained-release opioids should be used only for continuous pain.
- Opioids are generally recommended to reduce the level of moderate to severe pain.
- Opioids should be considered if reasonable, conservative therapy has been tried and has not been found to provide adequate relief.

1. American Academy of Pain Medicine and American Pain Society. The use of opioids for the treatment of chronic pain. Consensus statement from the American Academy of Pain Medicine and the American Pain Society. *Clin J Pain*. 1997;13:6-8.
2. Passik SD, Weinreb HJ. Managing chronic nonmalignant pain: overcoming obstacles to the use of opioids. *Adv Ther*. 2000;17(2):70-83.

Goals of Aggressive Pain Management for Chronic Pain

- Reduced pain levels
- Improved functionality ("up-time") and mood
- Better management of activities of daily living
- Return to work
- Reduced consumption of healthcare resources

- Effective management of chronic pain has become an increasingly critical issue in health care. Studies have shown that chronic pain is a common, persistent problem in the community with relatively high incidence and low recovery rates.[1]
  - Patients report that pain has a profound effect on their lives, restricting daily living and leisure activities. Since chronic pain has a profound effect on patients' lives, it is important that early diagnosis, treatment and referral to appropriate specialists be given high priority.[2]
- Failure to manage chronic pain aggressively may result in ongoing pain, poor functionality, and patient desocialization.
  - Clinical experience reveals that selection of an effective pain regimen for the patient with chronic pain, combined with aggressive management of side effects, leads to improved overall functioning and quality of life.

1. Elliott A, Smith B, Hannaford P, et al. The course of chronic pain in the community: results of a 4-year follow-up study. *Pain.* 2002;99:299.
2. McHugh G, Thoms G. Living with chronic pain: the patient's perspective. *Nurs Stand.* 2001;15:33-7.

Categories of Opioid Drugs

- Short-acting opioids
  - morphine sulfate (eg, Roxanol™, MSIR®)
  - codeine, (codeine sulfate, Tylenol with codeine®*)
  - hydrocodone (eg, Zydone®, Vicodin®, Lortab®, Vicoprofen®, Norco®)*
  - oxycodone (eg, Roxicodone™, Oxy IR®, Percocet®*, Tylox®*, Percodan®*)
  - hydromorphone (Dilaudid®)
  - oxymorphone (Numorphan®)
  - fentanyl (Actiq®)

* Contains additional active ingredient, amounts of which may vary.

- Short-acting opioids are appropriate for treatment of acute pain or breakthrough/incident pain, whereas long-acting formulations are used for patients with continuous chronic pain. Short-acting agents provide effective analgesia for acute pain but should be avoided as primary analgesics for chronic pain management. Short-acting opioids may be used during the initial dose titration period of long-acting formulations and as rescue medication for episodes of breakthrough/incidence pain.[1,2]
- Some short- and long-acting opioids may also contain other analgesics (eg, oxycodone/acetaminophen, hydrocodone/ibuprofen).

1. American Geriatric Society. Clinical Practice Guidelines. The Management of Chronic Pain in Older Persons. *J Am Geriatr Soc.* 1998;46:635-651.
2. McCarberg BH, Barkin RL. Long-acting opioids for chronic pain: pharmacotherapeutic opportunities to enhance compliance, quality of life, and analgesia. *Am J Ther*.

2001;8:181-186.

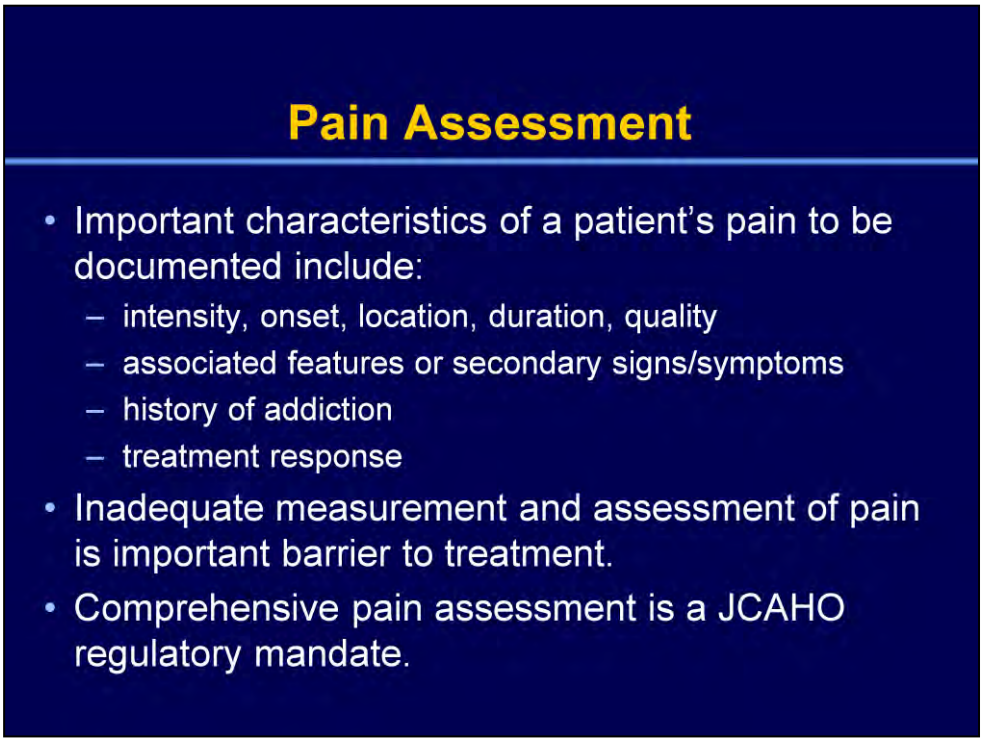
Categories of Opioid Drugs (cont)

- Long-acting opioids
  - methadone
  - sustained-release morphine (eg, MS Contin®, Avinza™; Kadian®, Oramorph©)
  - sustained-release oxycodone (OxyContin®)
  - transdermal fentanyl (Duragesic®)

- Long-acting opioids have greater utility than short-acting opioids in treating chronic pain in patients with consistent pain levels. Long-acting, controlled-release, oral formulations of opioids (eg, morphine, oxycodone), which have a predictable duration of action lasting from 8 to 12 hours, make around-the-clock therapy possible, offering dosing convenience, flexibility, and relative steadiness of the opioid concentrations in the blood.[1,2]

1. American Geriatric Society. Clinical Practice Guidelines. The Management of Chronic Pain in Older Persons. *J Am Geriatr Soc.* 1998;46:635-651.
2. McCarberg BH, Barkin RL. Long-acting opioids for chronic pain: pharmacotherapeutic opportunities to enhance compliance, quality of life, and analgesia. *Am J Ther*.

2001;8:181-186.



- One of the most important things a clinician can do to ensure accurate pain assessment is to monitor the patient's self-reported pain intensity.
- Comprehensive pain assessment is now a regulatory Joint Commission on Accreditation of Healthcare Organizations (JCAHO) mandate.
- Important characteristics of a patient's pain to be documented include[1,2] :
  - Onset, duration, location, distribution
  - Quality and intensity
  - Aggravating/relieving factors
  - Associated features or secondary signs/symptoms
    - neurologic deficit and hyperphenomena,
  - Associated factors
    - mood/emotional distress
    - functional activities—activities of daily living such as work or sleep
  - Treatment response
    - is pain adequately controlled?
    - breakthrough pain
      - end-of-dose failure
      - incident pain during specific activities known to exacerbate pain (which, when anticipated, can be pretreated)
      - spontaneous pain that is difficult to predict (common with neuropathic pain)
- Rational treatment cannot proceed without detailed records of previous treatments, including dosages, duration of therapy, side effects, and reason for stopping treatment.[1]

1. Backonja M-M, Galer BS. Pain assessment and evaluation of patients who have neuropathic pain. *Neurol Clin*. 1998;16:775-789.
2. Katz N. Neuropathic pain in cancer and AIDS. *Clin J Pain*. 2000;16(suppl 2):S41-S48.

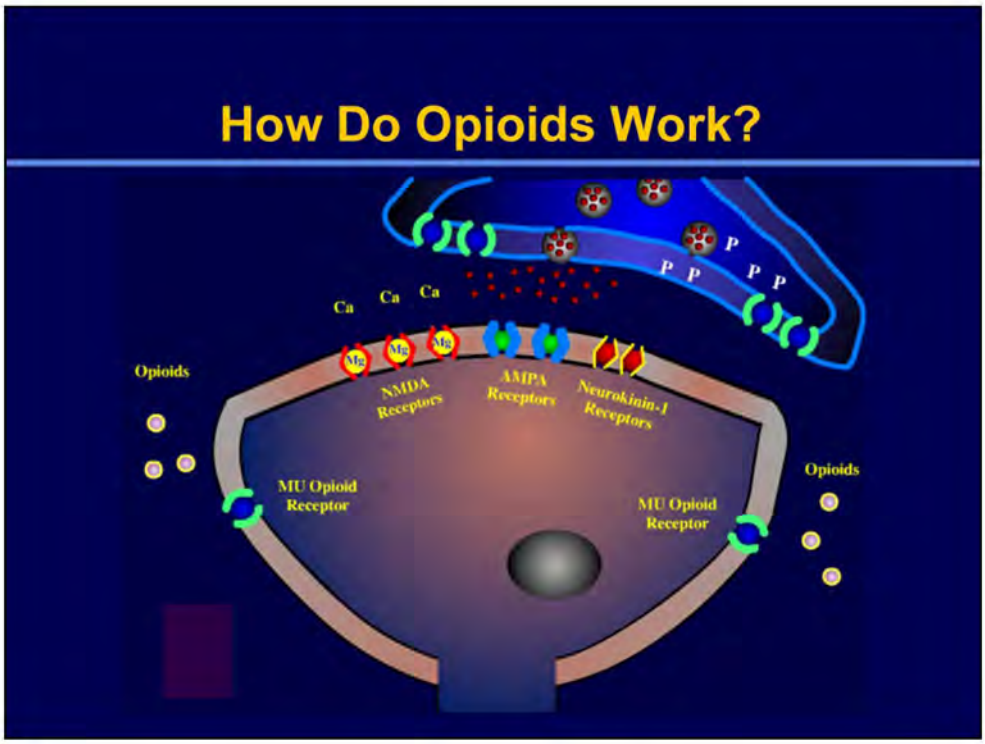
Opioids in Chronic Pain: Review of Randomized, Controlled Clinical Trials

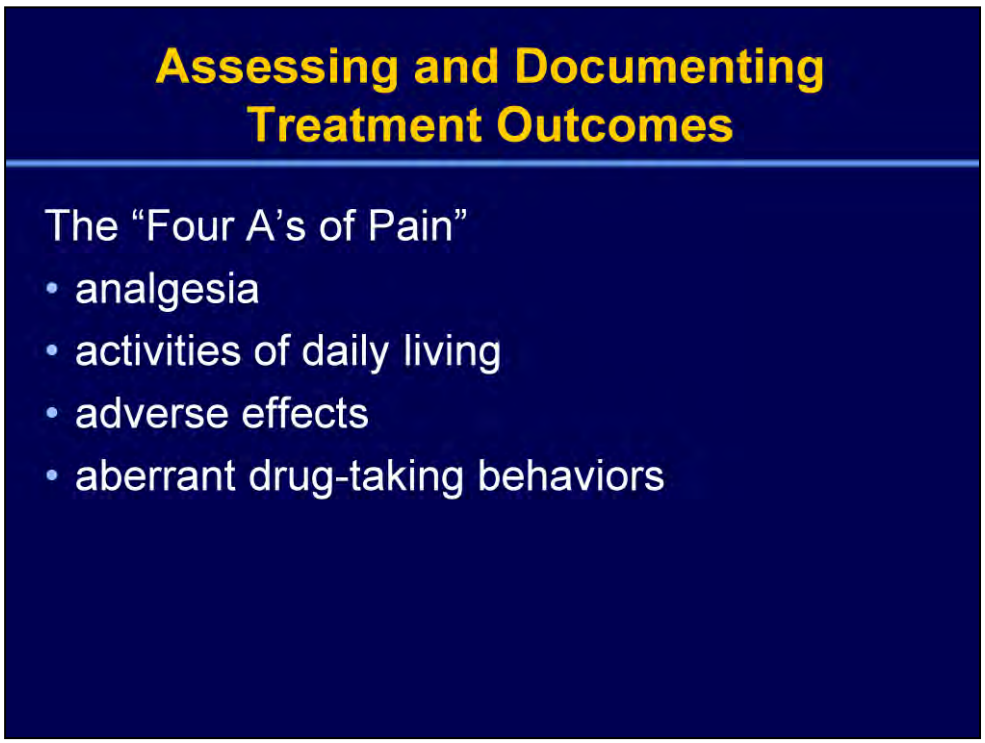
- Efficacy of opioids in chronic noncancer pain established in a number of randomized, controlled trials, including placebo-controlled trials of:
  - codeine
  - tramadol
  - oxycodone
  - morphine
  - fentanyl
- Comparative trial of transdermal fentanyl and sustained-release oral morphine

- The efficacy of opioids in chronic pain has been established in a number of randomized, controlled trials, including placebo-controlled trials of controlled-release oral codeine[1,2] and tramadol,[3] immediate- and sustained-release oxycodone,[4-6] intravenous and sustained-release oral morphine,[7-11] and fentanyl.[12]
- In a comparison of transdermal vs oral delivery, transdermal fentanyl and sustained-release oral morphine were compared in a crossover trial. In this study, a significantly greater number of patients (35% vs 23%; *P*=0.002) considered pain control better with transdermal fentanyl than with morphine.[8]

1. Peloso PM et al. *J Rheumatol.* 2000. 27:764-771.
2. Arkinstall W, et al *Pain.* 1995;62:169-178.
3. Harati Y et al. *J Diabetes Complications*. 2000;14:65-70.
4. Roth SH et al. *Arch Intern Med.* 2000;160:853-860.
5. Caldwell JR et al. *J Rheumatol.* 1999;26:862-869.
6. Watson CPN, Babul N. *Neurology.* 1998;50:1837-1841.
7. Caldwell JR et al. *J Pain Symptom Manage.* 2002;23:278-291.
8. Allen L et al. *BMJ.* 2001;322:1-7.
9. Jamison RN et al. *Spine.* 1998;23:2591-2600.
10. Moulin DE et al. *Lancet.* 1996;347:143-147.
11. Rowbotham MC et al. *Neurology.* 1991;41:1024-1028.

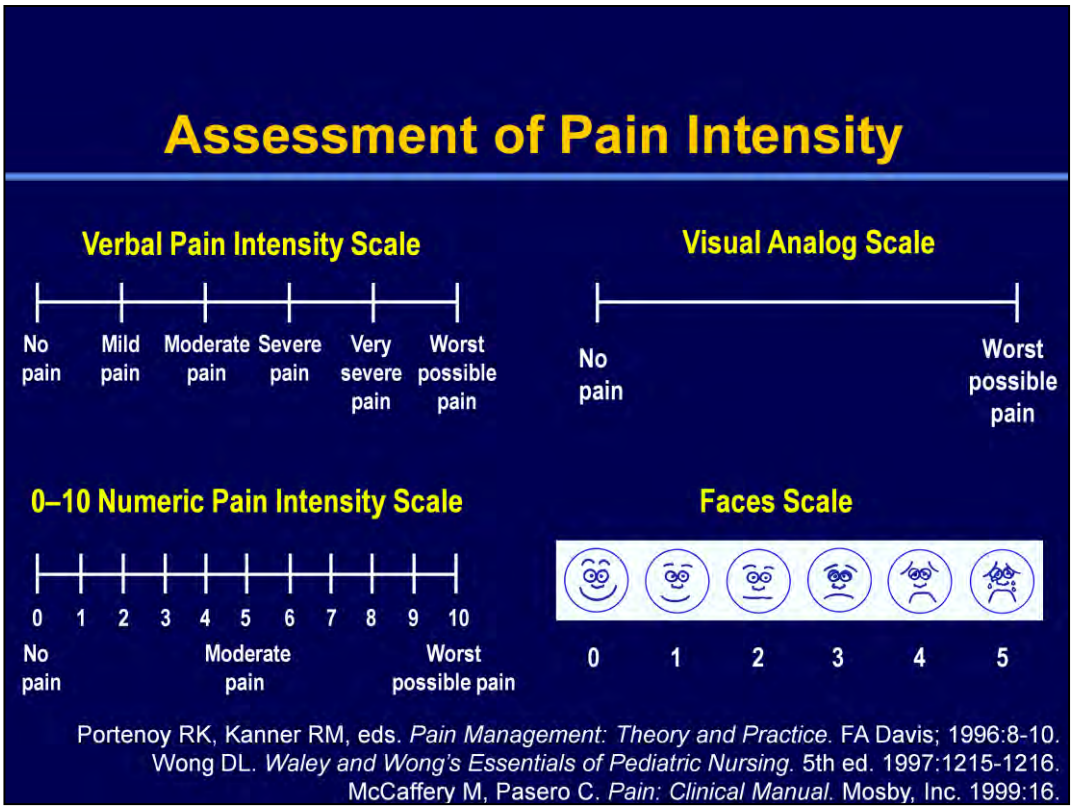
12. Dellemijn PL, Vanneste JA. *Lancet.* 1997;349:753-758.


How Do Opioids Work?
Ca
Ca
Ca
P
P
P
P
P
Mg
Mg
Mg
Opioids
NMDA Receptors
AMPA Receptors
Neurokinin-1 Receptors
MU Opioid Receptor
MU Opioid Receptor
Opioids



- The "Four A's" of outcome assessment are a useful approach for the physician to think about appropriate follow-up for optimal pain management.
- Although each of these four aspects will be discussed in detail in the following section, the key points include the importance of monitoring patients' pain intensity to ensure that they are receiving effective analgesia (pain relief), measuring effects on activities of daily living to document improvements in patient functioning (physical, psychosocial functioning), closely monitoring for adverse effects (side effects) in order to minimize or counter these effects, and being vigilant for any signs of aberrant drug taking (addiction-related outcomes) that may be preceding addiction or addiction-related behaviors.
- Most aberrant behaviors are not caused by addiction; clinical judgment is needed to differentiate these behaviors.
- Because pure mu-opioids do not possess a ceiling effect, the dose should be titrated until the patient experiences adequate pain relief or intolerable side effects. It is important to be aware that as the dose is escalated, the potential for side effects increases correspondingly. Therefore, the goal should be to optimize the therapeutic ratio.

Passik SD, Weinreb HJ. Managing chronic nonmalignant pain: overcoming obstacles to the use of opioids. *Adv Ther.* 2000;17:70-83.



- Addressing analgesia, the first of the "Four A's of Pain," requires an assessment of pain intensity to determine whether existing treatment is providing adequate relief. This slide depicts four of the pain scales that are used to assess a patient's pain. The scales are considered simple for patients to use as well as being valid methods for measuring the severity of pain.[1-3] These scales can be used at the patient's bedside, and patients can be asked to respond to either a spoken or written a question. The 0-10 numeric scale can be administered over the phone.
- With some scales, especially the visual analog scale, the patient marks the line at the point that best indicates the pain's intensity. Older patients may have difficulty using visual analog scales and it might be more appropriate to use a 0-10 numeric pain intensity scale.[4]
- The Wong-Baker FACES Pain Rating Scale is validated and recommended for patients aged 3 years or older. On this scale, Face 0 indicates no pain at all, Face 1 feels mild pain, Face 2 feels moderate pain, Face 3 feels severe pain, Face 4 feels very severe pain, and Face 5 feels the worst possible pain. The original appears above, and can be used as is or with the brief word descriptions under each number. In a study of 148 children aged 4 to 5 years, there were no differences in pain scores when children used the original or brief word instructions.[2]
- People with cognitive impairments and limited ability to communicate (eg, stroke patients) may have difficulty with the use of any self-report pain assessment scales. For these patients it will be necessary for the physician to rely on behavioral observation of patients' facial expressions, movement patterns (eg, bracing, guarding, distorted postures, avoidance of activity), and nonverbal sounds (eg, moans, winces) and reports of significant others (eg, partner, spouse, child) to make judgment of pain intensity.[5]
- However, remember that patient pain is multidimensional and involves more than just assessment of pain intensity.

1. Portenoy RK, Kanner RM. Definition and Assessment of Pain. In: Portenoy RK, Kanner RM, eds. *Pain Management: Theory and Practice*. Philadelphia, Pa: FA Davis Company; 1996:8- 10.
2. Wong DL. *Waley and Wong's Essentials of Pediatric Nursing.* 5th ed. St. Louis, Missouri: Mosby,

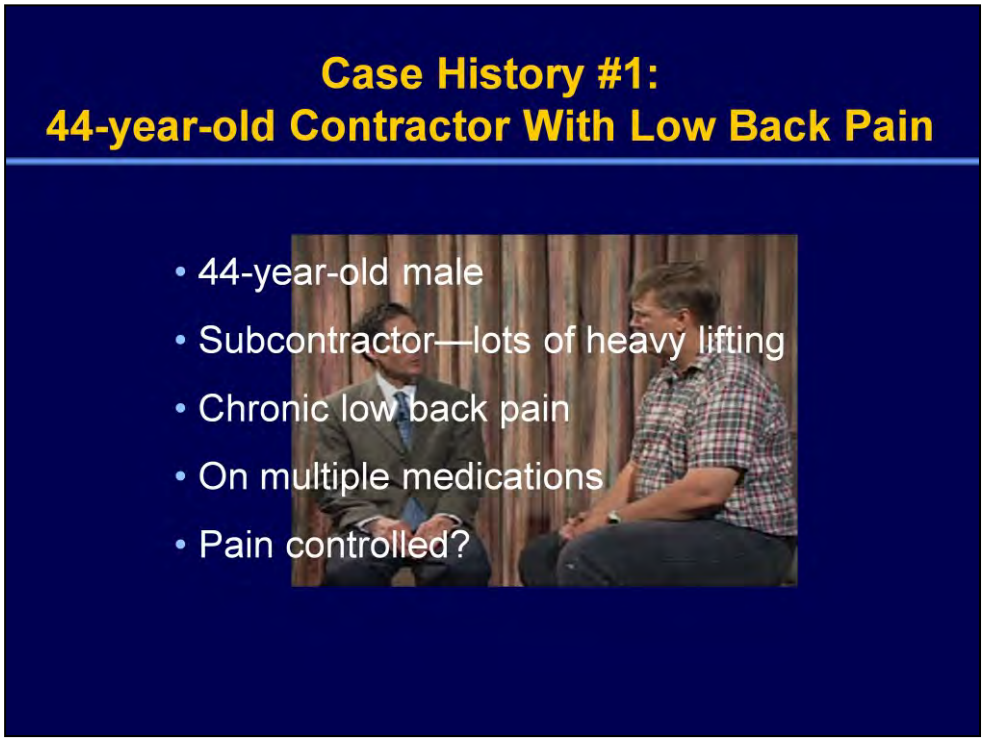
Inc.; 1997:1215-1216.
3. McCaffery M, Pasero C. *Pain: Clinical Manual.* St. Louis, Missouri: Mosby, Inc.;1999:16.
4. Jensen MP, Karoly P, Braver S. The measurement of Clinical pain intensity: a comparison of six methods. Pain. 1986;27:117-126.
5. Hadjistavropoulos T, von Baeyer C, Craig KD. Pain assessment in persons with limited ability to communicate. In: Turk DC, Melzack R, eds. *Handbook of Pain Assessment*. 2nd ed. New York, New York: Guilford; 2001:134-152.

- Quality of life is increasingly being recognized as one of the most important parameters to be measured in the evaluation of medical therapies, including those for pain management. Pain, when not effectively treated and relieved, has a detrimental effect on all aspects of quality of life. This negative impact has been found to span every age and every type and source of pain in which it has been studied. Effective analgesic therapy has been shown to improve quality of life by relieving pain.[1]

- Some clinicians have adopted the hospice concept of "total pain," in which the psychological, social, spiritual, and other aspects are emphasized. Particularly when it is chronic and related to advancing disease, pain can interact significantly with many facets of daily living. A holistic model of quality of life in such patients should, therefore, include a multidimensional or modular assessment of these areas, including the impact of pain on daily activities, mood, social relations, and sleep. Untreated pain associated with a patient's rehabilitation regimen may seriously inhibit or even prevent recovery.[2]

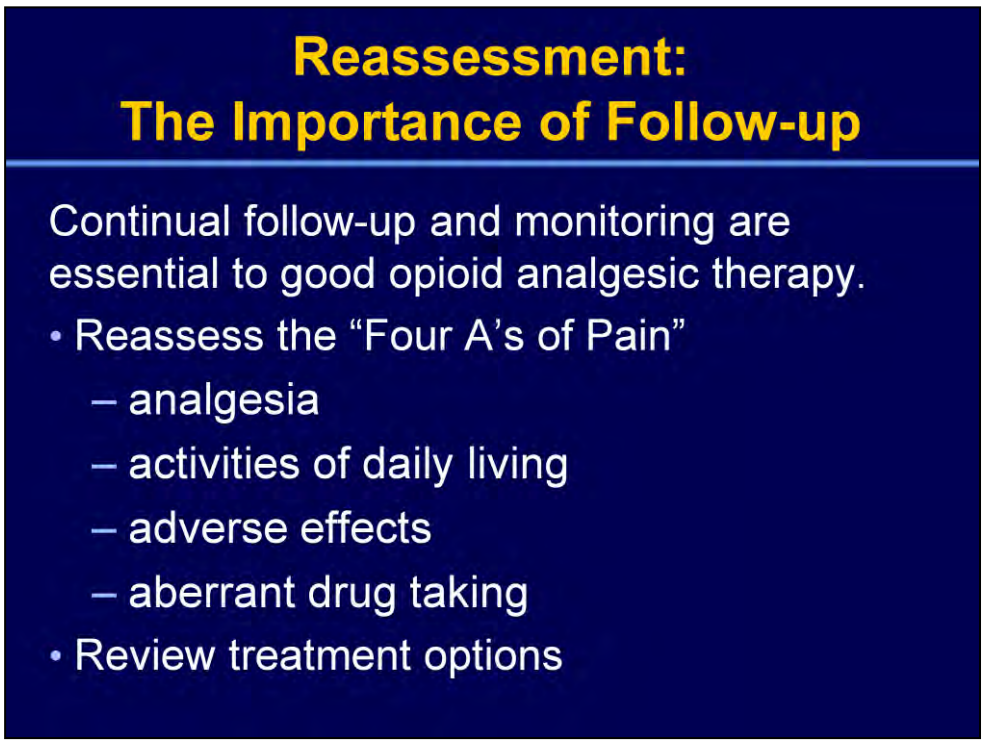
1. Katz N. The impact of pain management on quality of life. *J Pain Symptom Manage.* 2002;24(1 suppl):S38-S47.
2. Ahmedzai S. Recent clinical trials of pain control: impact on quality of life.

Eur J Cancer. 1995;31A (suppl 6):S2-S7.



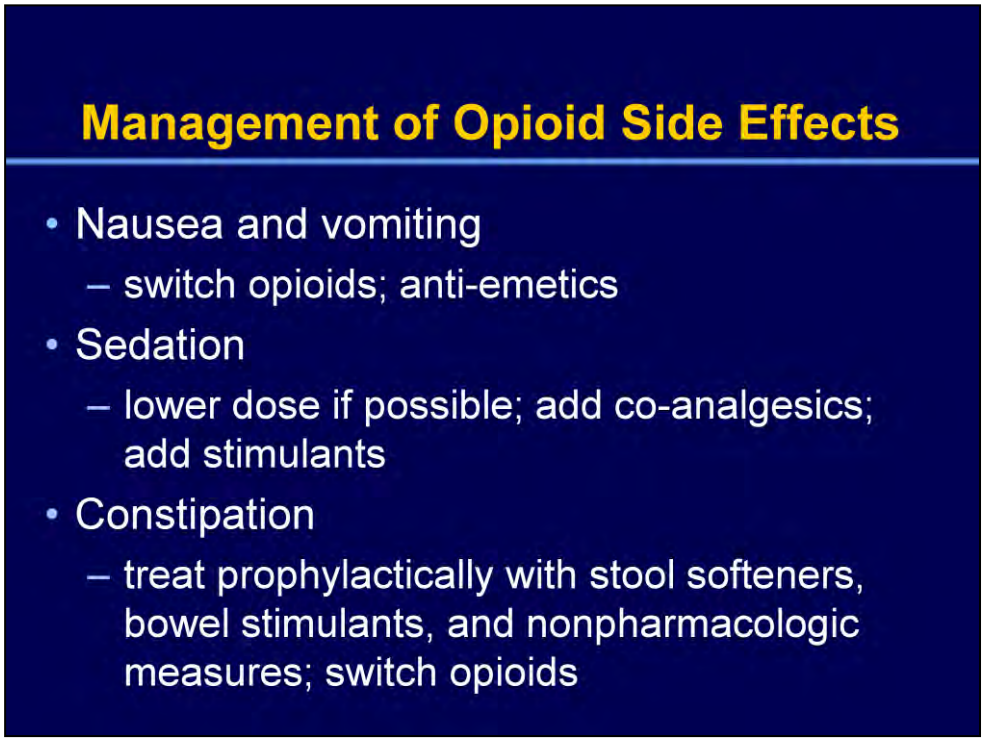
Instructions to presenter: *This slide has been created as an interactive tool for those choosing not to show the four previous video slides. If you choose to use this slide, please hide the previous four video slides; if you are showing the vignettes, please hide this slide.*

- This case history focuses on a patient whose pain levels, once well-controlled, have been increasing but who is resistant to the idea of increasing the dosage of his opioid medication.
- Part of the problem is the patient has been experiencing significant side effects, including constipation, swelling in the lower extremities, and daytime somnolence— which might be associated with opioids. But the patient's pain has been getting worse, the medicines being taken do not help as much as they had. Despite that, the patient resists the suggestion of more drugs or higher doses of drugs.
- Some patients may express a fear or dislike of medication. Even though chronic pain levels are increasing, these patients demonstrate a reluctance to increase the dose, or to switch to a stronger medication. This reluctance may be particularly acute with regard to opioids. Some patients fear addiction; or they attach a stigma to opioid use.
- Patients' perceptions and beliefs are integral to the decision-making process and ultimately the patient has the final say on his or her own care path.
- But having said that, it will be important to monitor this patient's pain levels, and perhaps to continue efforts to educate the patient and manage fears he may have that seem to cluster around certain chronic pain remedies.



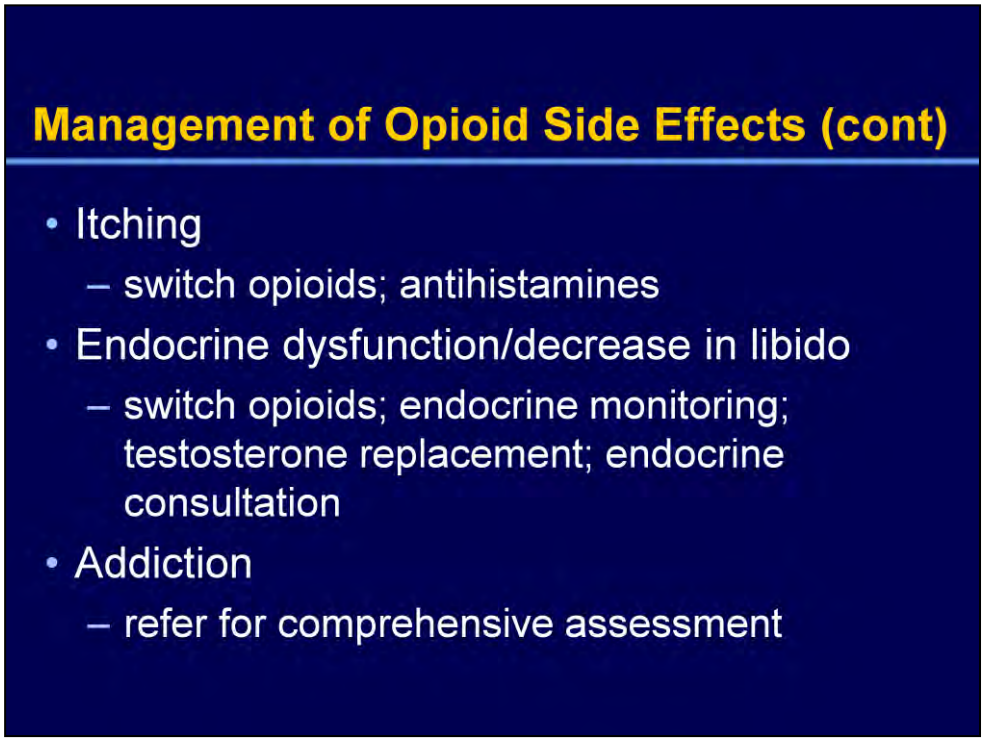
- Successful opioid therapy requires periodic review of patient status and achievement of therapeutic goals. While frequency of such assessments may vary from patient to patient based on case-specific characteristics (eg, severity of pain, difficulty of titration), it is important to keep track of how the patient is faring. Measuring the success of a pain management program should parallel the ways outcomes are measured in other chronic disease states (eg, diabetes). Although a reduction in pain scale numbers is important, it should also trigger critical thinking about impact of therapy on important functional outcomes.
- If during follow-up assessment it becomes clear that a particular opioid is not providing appropriate pain relief, a different opioid should be tried, keeping in mind that dosage conversion tables found in treatment guidelines should be used with care (they provide a guide, not an absolute). If this strategy is unsuccessful, the physician may need to determine if the patient needs to be referred to a pain specialist.
- Opioid rotation may be helpful in reducing side effects that may have developed with use of the opioid a patient is currently taking.
- It is important to assess the impact of opioid therapy on activities of daily living. Has the patient been able to return to work; is the patient comfortable at work? Is the therapy controlling pain, but making it more difficult to concentrate? Has the patient's socialization improved? If not, why not?
- Aberrant drug-taking behavior, if any, needs to be discussed and investigated. Is it a sign of addiction, or of inadequate pain management?
- A review of treatment options should periodically be undertaken. Well-controlled pain may provide an opportunity to titrate downward. Inadequate

pain control may suggest the need for a polypharmaceutical approach, especially if the pain is complex, with multiple underlying mechanisms.



- This slide addressed the management of adverse events associated with therapy.[1]
- Side effects, shown above in random order, may include nausea, vomiting, itching, sedation, balance/ataxia (especially in older patients) and pruritus. Cognitive impairments/mental "clouding" may also occur. However, tolerance to these side effects typically occurs within a few days to weeks of therapy initiation. The most common side effect of chronic opioid therapy is constipation, which may persist, particularly if there are other predisposing causes.
- Once ruling out other causes, opioid side effects may be ameliorated by a number of approaches. For nausea, first try switching opioids and then try anti-emetics. For nausea associated with vertigo or movement, try antivertiginous agents (eg, scopolamine); for nausea associated with satiety, try metoclopramide.
- For sedation/somnolence, lower dose if possible; or add co-analgesics or psychostimulant agents. Modifications in the patient's diet and activity levels may also be beneficial.
- For constipation, treat prophylactically with stool softeners, bowel stimulants, and nonpharmacologic measures or try switching opioids.

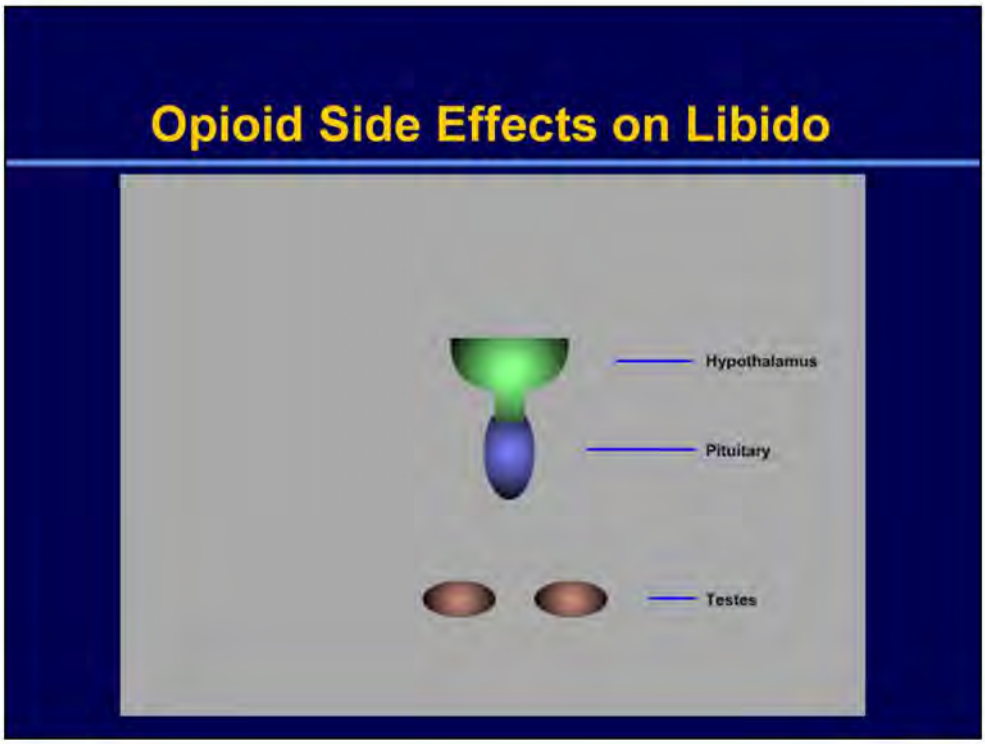
1. Portenoy RK. Opioid analgesics. In: Portenoy RK and Kanner RM, eds. *Pain Management: Theory and Practice*. Philadelphia, PA: F.A. Davis Company;1996:248-253.

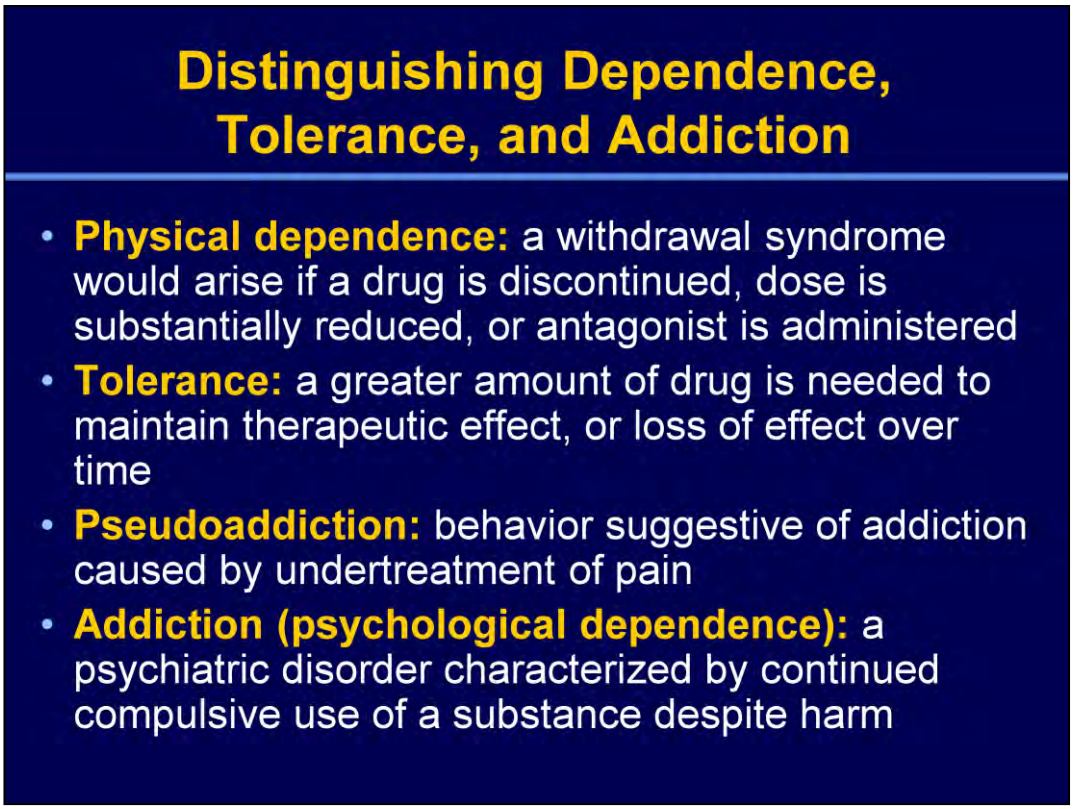


- It is critical to once again address the importance of titration.Titration of dose is key to achieving optimal balance between therapeutic analgesics and side effects.
- Long-term administration of intrathecal opioids may also be associated with decreased libido, as a result of opioid effects on the hypothalamic-pituitary-gonadal axis (leading to hypogonadotrophic hypogonadism). Thus, such patients may need endocrine monitoring, consider testosterone replacement, or switching opioids; consider endocrine consultation.[1-3]
- Opioid therapy may be especially problematical in certain categories of patients—those engaged in high-risk activities or occupations and those with histories of substance abuse. Use caution and clinical judgment. Consult with a pain specialist. It is useful to develop a relationship with a pain specialist—even prior to the occurrence of a need to refer.

1. Abs R, Verhelst J, Maeyaert J, van Buyten J-P, Opsomer F, Adriaensen H, Verlooy J, et al. Endocrine consequences of long-term intrathecal administration of opioids. *J Clin Endocrinol Metab.* 2000;85:2215-2222.
2. Finch PM, Roberts LJ, Price L, Hadlow NC, Pullan PT. Hypogonadism in patients treated with intrathecal morphine. *Clin J Pain.* 2000;16:251-254.
3. Roberts LJ, Finch PM, Pullan PT, Bhagat CI, Price LM. Sex hormone suppression

by intrathecal opioids: a prospective study. *Clin J Pain.* 2002;18:144-148.


Opioid Side Effects on Libido
Hypothalamus
Pituitary
Testes

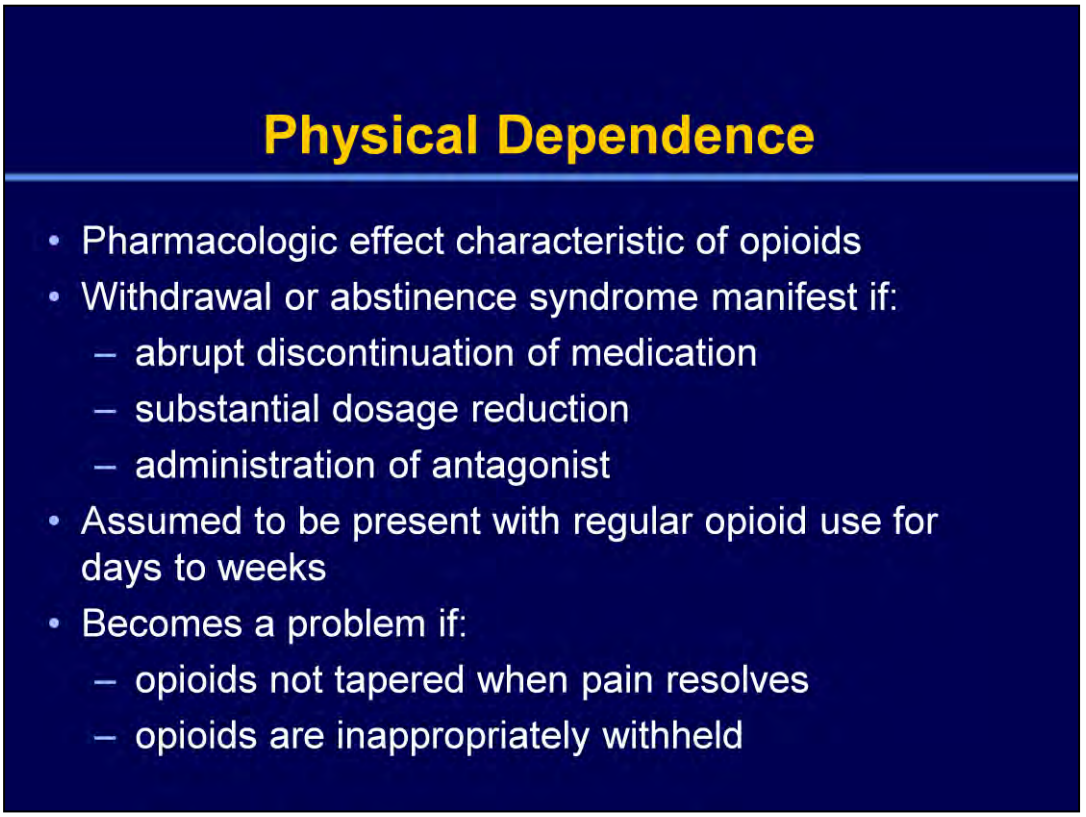


- This slide addresses the issue aberrant drug-taking behaviors.
- Before considering initiation of opioid treatment, it is important for the physician, patient, and family to understand the distinction between physical dependence, tolerance, and addiction.
- Physical dependence is a pharmacologic effect characterized by the development of a withdrawal syndrome when an opioid drug is discontinued, when the dose is substantially reduced, or if an antagonist is administered. Dependence occurs in almost all patients on opioids and does not connote addiction.[1]
- Tolerance means that a greater amount of drug is needed over time to maintain a therapeutic effect. The number of patients who develop clinically relevant tolerance is unknown. Tolerance may also occur to side effects, and thus may be beneficial. Some patients who develop tolerance may be managed by judicious dose increases[2]; others who develop inexorable tolerance cannot be managed on opioids. There is no evidence to support a role for analgesic tolerance in the development of drug addiction. Addiction is, however, often though not always associated with tolerance.
- Pseudoaddiction refers to behaviors suggestive of addiction (eg, multiple prescribers, hoarding) when patients are undertreated for pain.[1]
- Addiction is a psychiatric disorder consisting of continued, compulsive use of the substance despite harm.[1] The *Diagnostic and Statistical Manual of Mental Disorders* provides nine categories of opioid use or opioid-induced disorders, including diagnostic criteria for opioid dependence or opioid abuse.[3]
- True addiction (patient loss of control) may become obvious only when the physician stops prescribing the medicine. There is, however, there is little evidence that addictive behaviors are common within the chronic pain population. In a study reviewing the available data, it was found that prevalence estimates for addiction in patients with chronic pain ranged from 3% to 19%.[4]

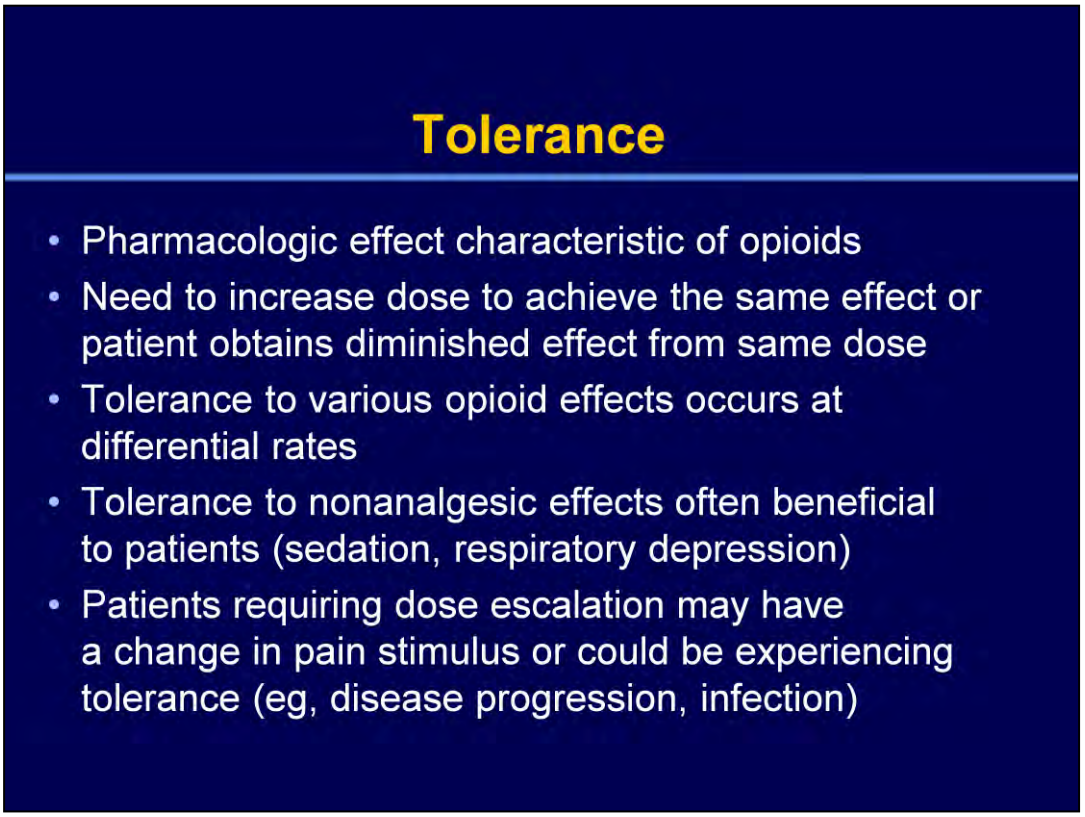
1. American Academy of Pain Medicine, American Pain Society, American Society of Addiction Medicine. *Definitions Related to the Use of Opioids for the Treatment of Pain*. 2001. Available at: http://www.ampainsoc.org/advocacy/opioids2.htm. Accessed October 2, 2002.
2. Zenz M. Morphine myths: sedation, tolerance, addiction. *Postgrad Med J*. 1991;67:S100-S102.
3. American Psychiatric Association. *Diagnostic and Statistical Manual of Mental Disorders.* 4th Ed. Rev Ed. Washington, DC: American Psychiatric Publishing, Inc.; 2000:269-277.
4. Fishbain DA, Rosomoff HL, Rosomoff RS. Drug abuse, dependence, and addiction in chronic pain patients. *Clin J Pain.* 1992;8:77-85.

- In assessing aberrant drug-taking behaviors in the context of the pain clinic setting, certain behaviors are probably more predictive of risk for true drug addiction problems than others.
- Some of the more predictive behaviors, many of them illegal, include selling prescription drugs, forging prescriptions, stealing or borrowing another patient's drugs, injecting an oral formulation, obtaining prescription drugs from nonmedical sources, concurrent abuse of related illicit drugs, multiple unsanctioned dose escalations, or recurrent prescription losses.[1,2]
- On the other hand, aberrant behaviors such as aggressive complaining about needing higher doses, drug hoarding, requesting specific drugs, acquisition of similar drugs from other medical sources, unsanctioned dose escalation on one or two occasions, unapproved use of the drug to treat another symptom, or reporting unintended psychic effects, may not be as predictive for drug abuse concerns.[1,2]
- Because some degree of noncompliant behavior is common among patients in clinical practice, it is important to consider not only the type of behavior but also the frequency or number of aberrant behaviors occurring in an individual patient when assessing a potentially problematic situation.

1. Passik SD, Portenoy RK, Ricketts PL. Substance abuse issues in cancer patients. Part 1: Prevalence and diagnosis. *Oncology*. (Huntingt). 1998;12:517-521, 524.
2. Passik SD, Portenoy RK, Ricketts PL. Substance abuse issues in cancer patients. Part 2: Evaluation and Treatment. *Oncology*. (Huntingt). 1998;12:729-734, 736, 741-742.



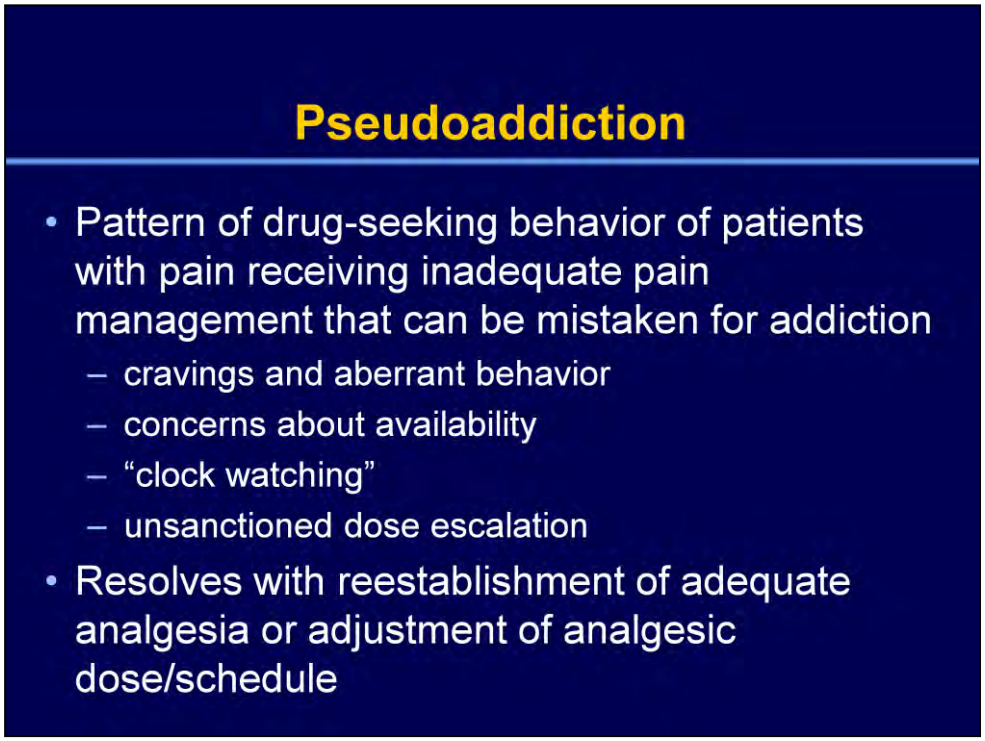
- The truly opioid-addicted patient will require extensively structured pain management programs to address these abuse issues while still providing adequate pain treatment.
- However, it is crucial to distinguish between true addiction/abuse and the characteristics of physical dependence and tolerance inherent in opioid use, as there is often confusion among both patients and physicians regarding these issues.
- Physical dependence is not addiction (and the terms should not be used interchangeably). Physical dependence is a pharmacologic effect characteristic of a number of different types of medications. Physical dependence is defined as the occurrence of an abstinence syndrome (withdrawal reaction) following abrupt discontinuation of the drug, substantial dose reduction, or administration of an antagonist.
- This is generally assumed to occur with regular opioid use for as brief a period as a few days.
- However, physical dependence does not become a problem in the clinical setting unless patients are not instructed to taper the dose when discontinuing treatment or if opioids are inappropriately withheld.
- It is important to remember that all clinical medicine balances therapeutic effects with adverse effects. Adverse effects may occur, and must be recognized and balanced, but their possible, or even actual, occurrence is not a reason to avoid the pharmacologic treatment unless they are clinically unmanageable or intolerable to the patient.



- Addiction is also not synonymous with tolerance. Tolerance, too, is a pharmacologic effect characteristic of opioids, defined as the need to increase the dose to achieve the same effect or the experience of a diminished effect from the same dose.
- Tolerance means that increasing doses of opioid analgesics are required to maintain the original therapeutic effect. This is a common occurrence in patients of all age groups taking opioid analgesics chronically. The first sign of the development of tolerance may be a decrease in the duration of effective analgesia.
- Tolerance is a physiologic event that should be addressed from a neurophysiologic perspective, as well as taking into account the patient's clinical response.
- Tolerance to various opioid effects occurs at differential rates, and tolerance to the side effects of opioids (eg, sedation, respiratory depression) can actually be beneficial to patients.
- There is no evidence to support a role for analgesic tolerance in the development of drug addiction. Addiction is, however, often though not always associated with tolerance.

American Pain Society Quality of Care Committee. Quality improvement guidelines for the treatment of acute pain and cancer pain. *JAMA*. 1995;274:1874-1880.

American Pain Society (APS): www.ampainsoc.org/



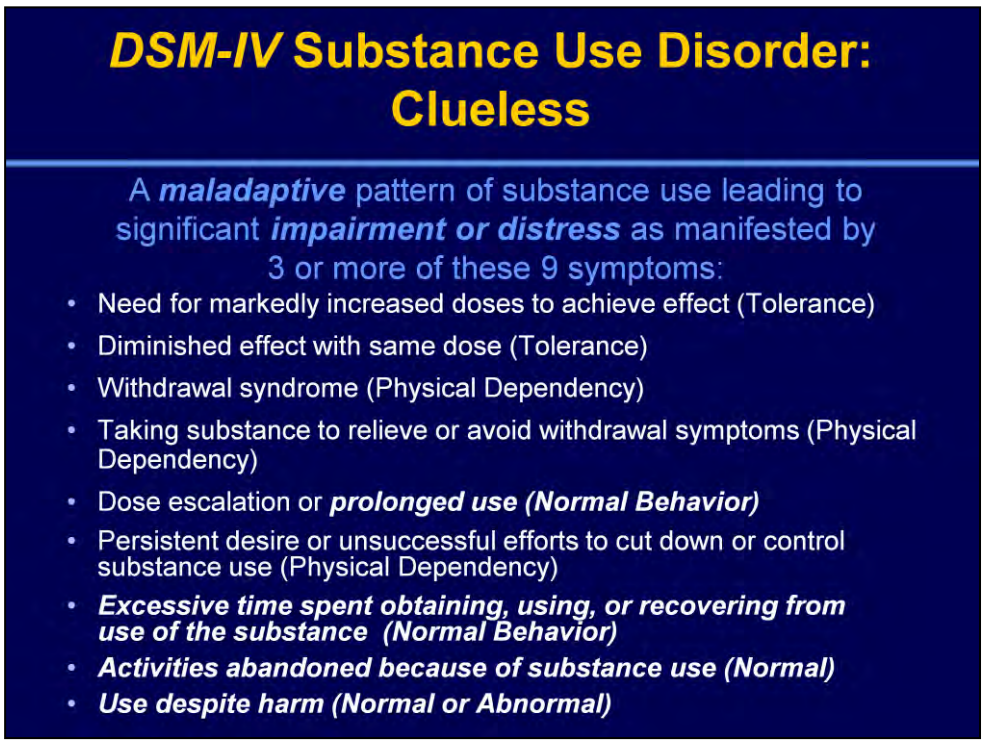
- For patients with continuous pain, inadequate pain management (eg, as-needed dosing schedule, use of drugs with inadequate potency, use of dosing intervals that are too long) can lead to behavioral symptoms that mimic those seen with psychological dependence and can be mistaken for addiction.
- These may include cravings and aberrant behavior, concerns about availability, clock watching, and unsanctioned dose escalation.
- In the case of pseudoaddiction, the problem behaviors resolve after sufficient pain relief is established.
- However, behaviors related to true addiction may also resolve after dose escalation.
- Thus, it can be difficult to distinguish pseudoaddiction from true addiction, and may require careful balancing until the circumstances are sorted out. For example, it may be helpful to raise the dose and switch to a long-acting opioid but only give the patient a week's prescription at a time.

Weissman DE, Haddox JD. Opioid pseudoaddiction—an iatrogenic syndrome. *Pain.* 1989;36:363-366.

Differential Diagnosis of Aberrant Drug-Taking Attitudes and Behavior

- Addiction
- Pseudoaddiction (inadequate analgesia)
- Other psychiatric diagnosis
  - encephalopathy
  - borderline personality disorder
  - other personality disorder
  - depression
  - anxiety
- Criminal intent or TDFO

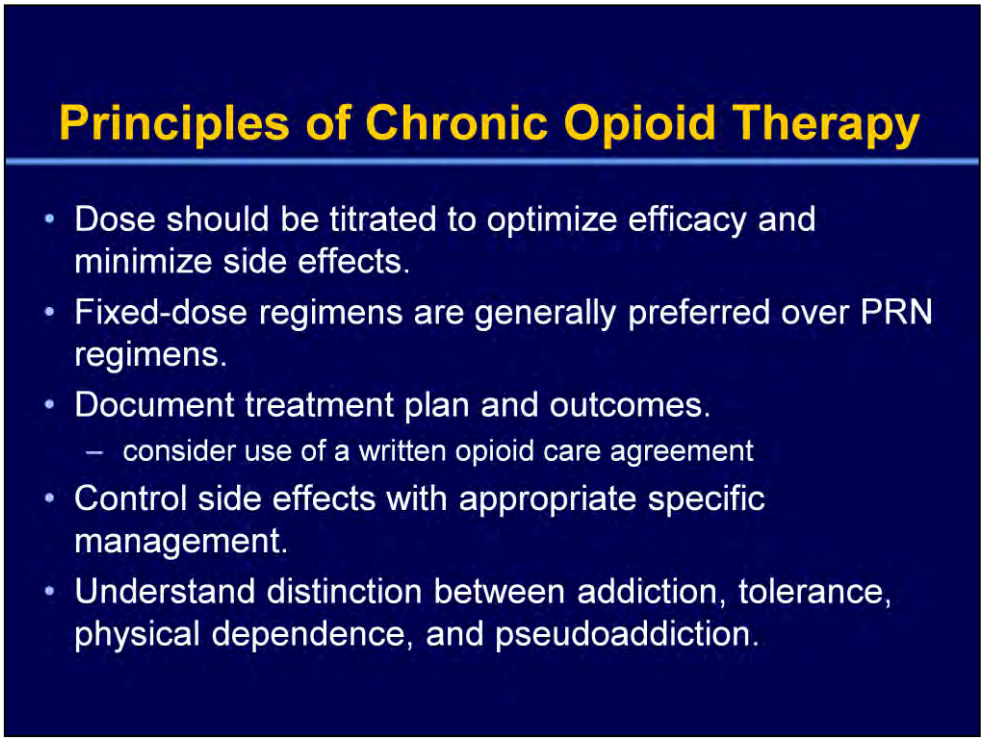
- Because no specific set of aberrant drug-taking behaviors has a particular linkage to addiction, careful differential diagnosis of such behavior is key. When aberrant behavior is noticed in the clinic, it is essential to have the vocabulary to talk to patients about non-compliance and then to try to determine what type of problem is underlying the behavior.
- If true addiction were suspected, patients may need more structured treatment management and limited amounts of drug per prescription, and often will require referral to pain specialists or addictionologists.
- For patients who seem to be suffering from pseudoaddiction, an increased dose may be required.
- Patients with other psychiatric diagnoses, who fall generally into the category of “chemical copers” and may be overly drug-focused, self-medicating symptoms of depression or anxiety, or struggling with personality issues/situational stresses. They usually need primary treatment for those underlying problems as well as more structured pain treatment.
- Finally, there are patients who criminally divert opioid prescription medications, which can be very difficult to detect.
- These behaviors have not been systematically studied, and there are no doubt other causes than those listed here.



- Another criterium utilized for determining substance abuse disorders is the DSM-IV. The DSM-IV criteria for substance use disorder are presented in this slide, where the disorder is defined as a maladaptive pattern of substance use leading to significant impairment or distress including 3 of the 9 symptoms listed.
- Particular “red flags” include excessive time spent obtaining, using, or recovering from use of the substance, abandoning usual activities because of the substance use, loss of control over the use of the substance, and use of the substance despite harm.
- *DSM-IV* criteria for Substance Use Disorders have not been validated in patients with chronic pain and are of doubtful utility in this population—at least 3 of the diagnostic criteria for this disorder (**not italics**) would occur during the normal use of long-term opioids for chronic pain.

- Because individual patient circumstances and responses to pain and treatments vary widely, it is crucial to tailor the approach to pain management for individual patient needs.
- The level of structure and monitoring required for managing patients receiving long-term treatment with opioids can range anywhere from minimal for the uncomplicated patient to providing psychological support for "chemical copers" with comorbid psychiatric difficulties to highly structured programs for actively or recovering addicted patients.
- Many patients will require minimal structure because of a lack of comorbid medical, psychiatric, or substance abuse problems, and lack of contact with addiction subculture.
- Treatment decisions for chronic noncancer pain patients may vary from those decisions made for patients with cancer pain. Concerns about addiction, tolerance, and side effects must be viewed differently.
- Chemical copers may resemble addicts with regard to the "centrality" of the drug and drug procurement. They need structure, psychiatric input, and drug treatments that *decentralize* the pain medicine to their coping.
- Patients may migrate among these "types" or syndromes over time; such changes must be monitored and documented.
- Since the borders and defining characteristics of these syndromes have not been unequivocally established, clinicians have the responsibility to use their best judgment.
- Complicated patients should be referred to pain specialists and/or addictionologists.

- Physicians must be aware that it is LEGAL to prescribe opioids to patients with addiction FOR THEIR PAIN; it is not legal to prescribe opioids to a patient FOR THEIR ADDICTION (except in a licensed methadone maintenance center), regardless of whether they have pain.



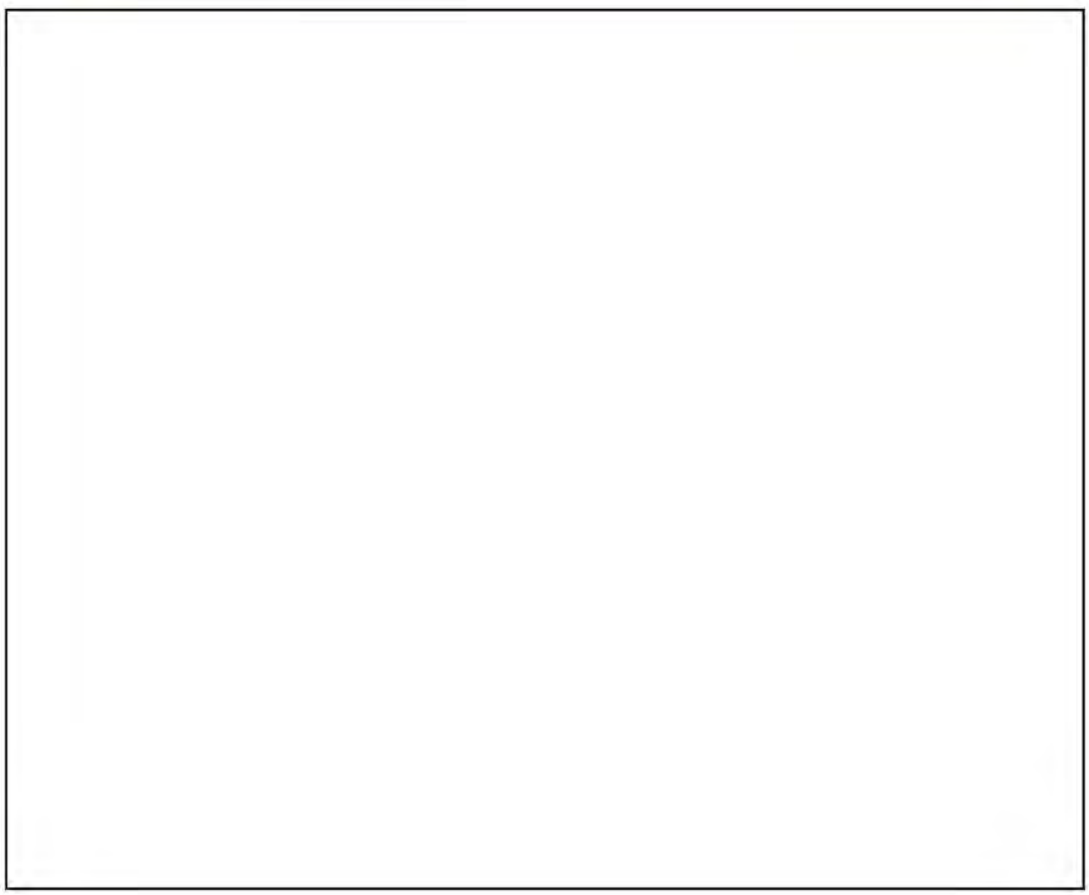
- Opioid therapy entails a number of risks for patients, but these potential problems can be prevented or circumvented.
- Documentation is critical and should include the initial evaluation, substance abuse history, psychosocial issues, pain/pain relief, side effects, functional outcomes, and continuing monitoring. Regular discussions with family members about the patient's condition and use of opioids can improve the accuracy of monitoring.[1]
- The laws on patient monitoring vary from state to state, but the federal government regulates and legislates the use of controlled substances and drugs. Generally, federal laws have priority over state laws.[2]
- Most opioid side effects can be controlled with appropriate specific management (eg, prophylactic bowel regimens, use of stimulants).[1,3]
- There is a chance that patients on opioids or those who appear to require them may also develop or have significant psychosocial rehabilitative issues. In such cases, these patients are generally best referred to a multidisciplinary center with experience managing chronic pain with opioids.[1]

1. Pappagallo M. Aggressive pharmacologic treatment of pain. *Rheum Dis Clin North Am*. 1999;25:193-213.
2. Clark HW. Policy and medical-legal issues in the prescribing of controlled substances.
J Psychoactive Drugs. 1991;23:321-328.
3. Zenz M. Morphine myths: sedation, tolerance, addiction. *Postgrad Med J*.

1991;67:S100-S102.

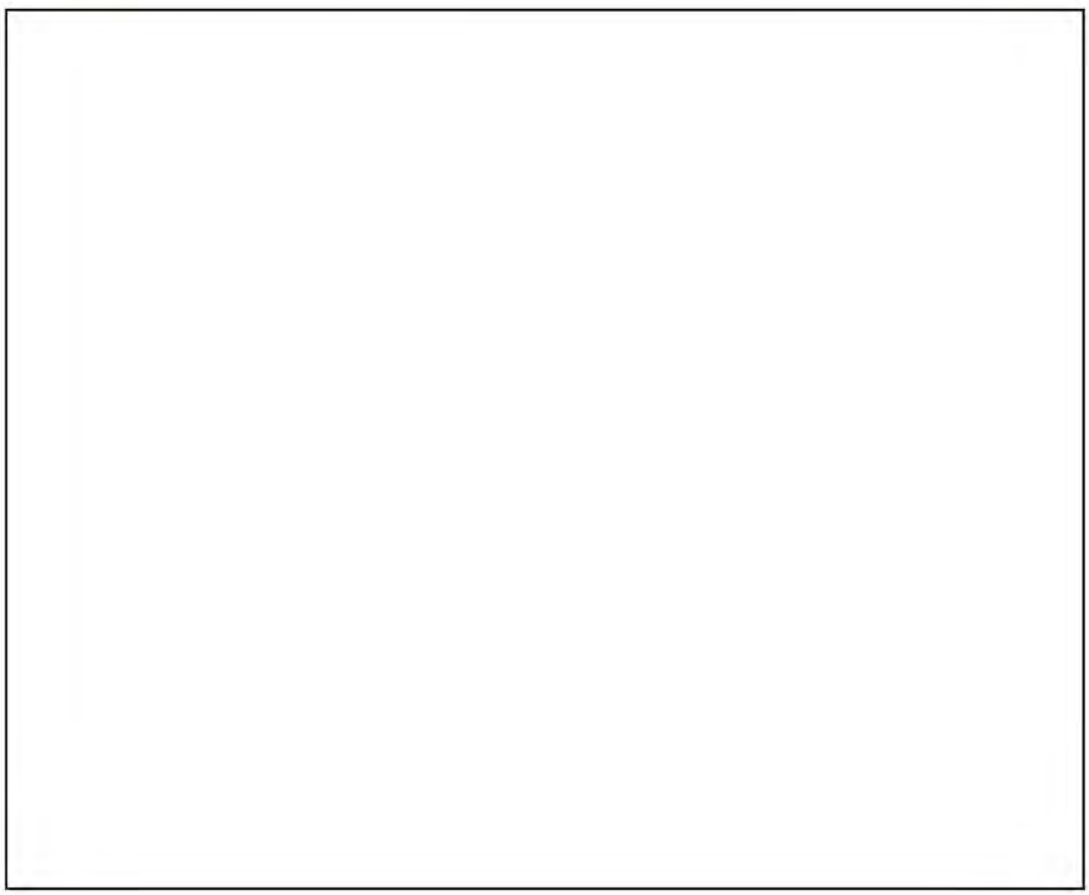
Principles of Opioid Therapy

- Opioids should be balanced with other treatment.
  - medications
  - invasive treatments
  - nonmedication modalities
  - psychosocial support
  - education about pain
  - cognitive approaches focused upon an active lifestyle

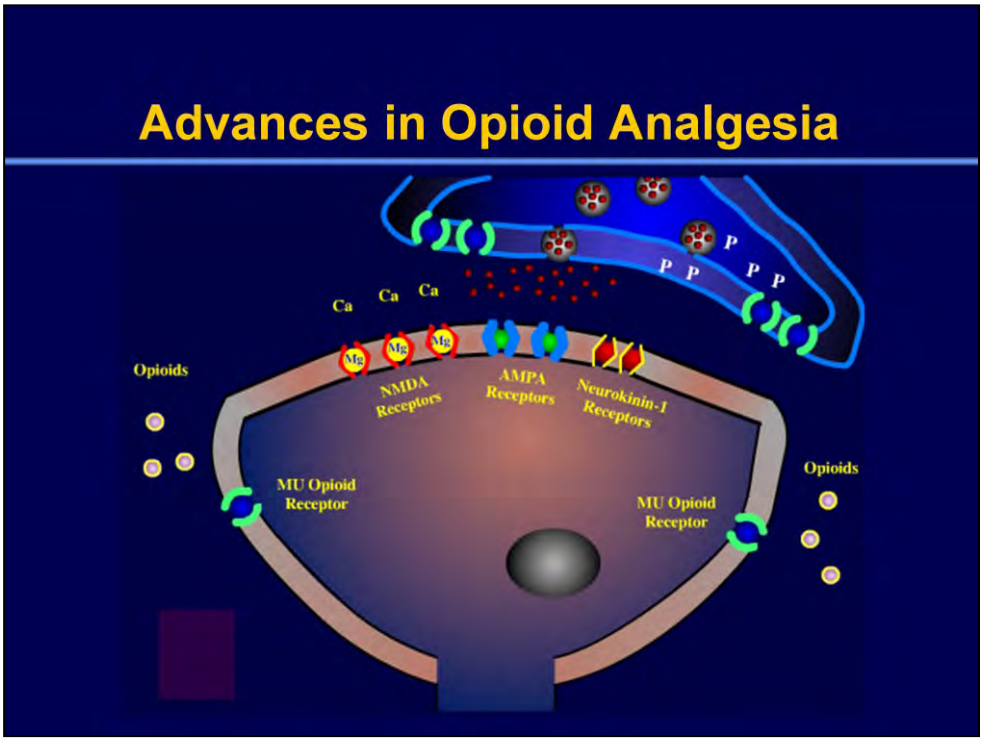


Case History #2: 44-year-old Woman With HNP of Lumbar Spine

- 44-year-old woman with HNP of lumbar spine, neuropathic pain, foot drop, facet arthropathy
- Treated with lumbar fusion
- Complex rational polypharmacology includes long-acting morphine 540 mg/d, oxycodone for breakthrough pain, Valdecoxib for inflammatory pain, Clonazepam for opioid-induced myoclonus, Modafinil for drowsiness, and Tiagabine for neuropathic pain and wind-up pain
- Patient has had facet neurotomies every 6 months for the last 7 years

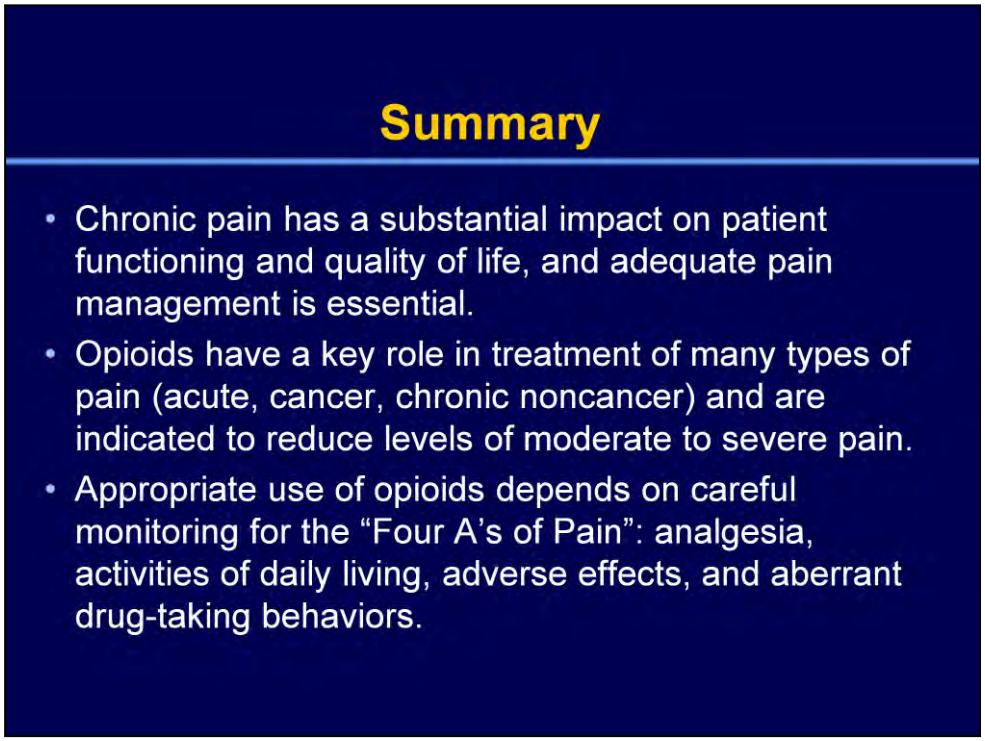


- Thus far, we have discussed optimizing the use of the opioid analgesics we have available to us in clinical practice today. By utilizing the principles we have discussed, you can provide effective analgesia to your patients while minimizing opioid-related side effects. You can also help address patient concerns about the risk of addiction or the fear of development of analgesic tolerance that might prevent ongoing, effective pain control.
- Meanwhile, ongoing clinical research continues to pursue additional means by which opioid therapy can be improved.



Instructions to presenter: *The first thing to understand about this animation is that all roads lead back to the initial screen. All animations have stop action and further buttons that lead to next steps. To make the animation live, click anywhere on the screen. Move the cursor over a button and a pointing finger will appear and the button will change color. Detailed lecture notes for each animated "click" appear in the file "04 Notes for Slide 52 (animation).doc" on the CD.*

- Interestingly, some of the same pathways involved in central sensitization are also involved in the potential development of opioid analgesic tolerance.



- Because of the substantial impact of chronic pain on patient functioning and quality of life, as well as negative effects on families and society at large, adequate pain management is essential.
- Opioids are a mainstay of treating all types of pain, both acute and chronic pain, cancer related or noncancer related, and treatment guidelines indicate their use when pain is moderate to severe.
- Although physicians are often reluctant to prescribe opioids, they can be safely and appropriately used with attention to monitoring patient outcomes, based on the "Four A's of Pain":
  - analgesia
  - activities of daily living
  - adverse effects
  - aberrant drug taking

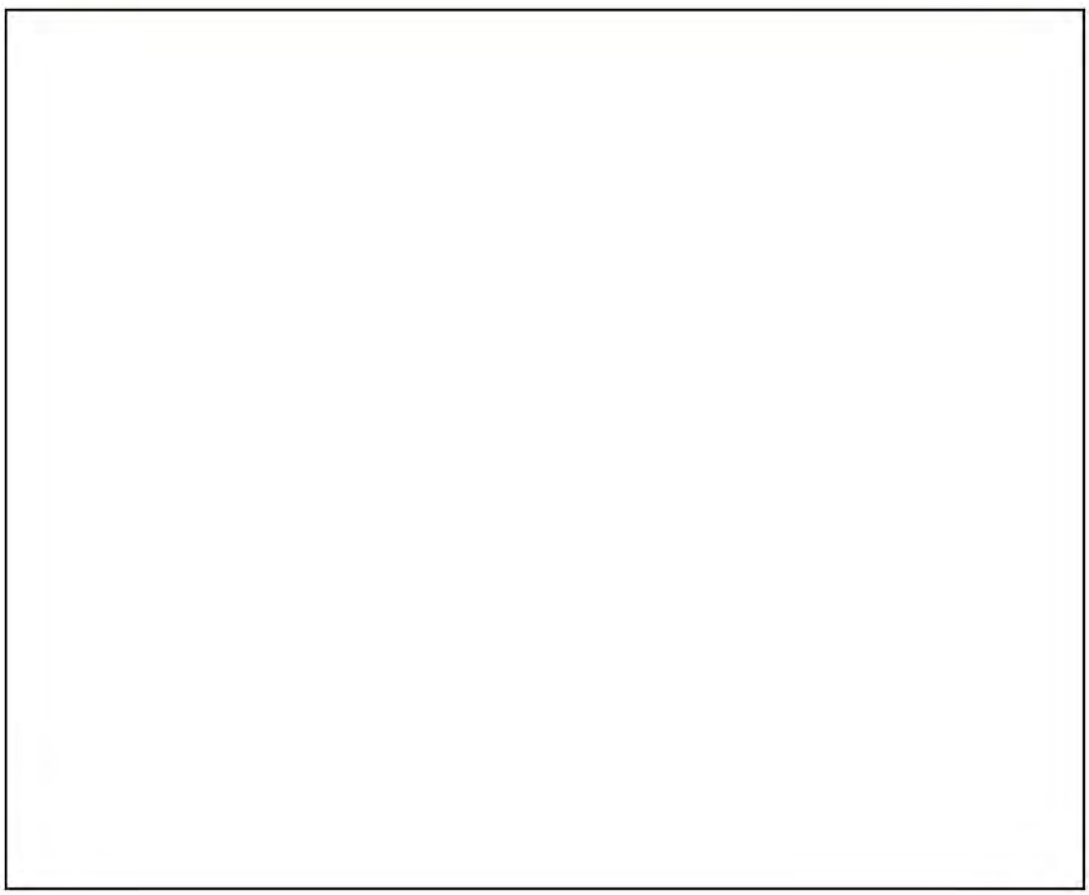
Summary (cont)

- Like all therapies, opioids can be associated with complications that must be monitored, diagnosed, and rationally managed.
- With proper patient management, opioids are an essential tool to help achieve successful control of chronic pain.

Case Discussion

Advances in Opioid Analgesia:
Maximizing Benefit, Minimizing Harm


THOMSON
PROFESSIONAL
POSTGRADUATE SERVICES
New Directions in Pain Management: Emerging Therapies
Jianren Mao, MD, PhD
MGH Pain Center
Massachusetts General Hospital
Harvard Medical School
Boston, Massachusetts



Mu-Opioid Receptor Polymorphisms

Mu-opioid receptor exhibits dozens of polymorphisms which may:

- appear to increase risk of drug abuse
- protect against opioid side effects
- alter patient responses to opioid analgesia

- A high number of polymorphisms have been detected in the mu-opioid receptor (MOR), some of which may underlie some of the interindividual response variability to different opioids.[1]
  - The polymorphism at position A118-G in the human MOR gene may have implications for opiate addiction.[2] It may also be protective against morphine-6-glucuronide (M6G) opioid toxicity and side effects. M6G is the active metabolite of morphine.[3]
  - Carriers of other mutant MOR alleles might display altered responses to narcotic analgesics.[4]
  - The S268P mutation in the third intracellular loop of the MOR gene appears to represent a loss-of-function mutation for the human MOR. That could result in a reduction in the efficacy and potency of several opioid agonists.[5]

1. Mayer P, Hollt V. Allelic and somatic variations in the endogenous opioid system of humans. *Pharmacol Ther*. 2001;91:167-177.
2. Bond C, LaForge KS, Tian M, et al. Single-nucleotide polymorphism in the human mu opioid receptor gene alters beta-endorphin binding and activity: possible implications for opiate addiction. *Proc Natl Sci USA*. 1998;95:9608-9613.
3. Lotsch J, Zimmermann M, Darimont J, et al. Does the A118G polymorphism at the mu-opioid receptor gene protect against morphine-6-glucuronide toxicity? *Anesthesiology*. 2002;97:814-819.
4. Wang D, Quillan JM, Winans K, et al. Single nucleotide polymorphisms in the human

mu opioid receptor gene alter basal G protein coupling and calmodulin binding. *J Biol Chem*. 2001;276:34624-34630.

5. Befort K, Filliol D, Decaillot FM, et al. A single nucleotide polymorphic mutation in the human mu-opioid receptor severely impairs receptor signaling. *J Biol Chem*. 2001;276:3130-3137.

Peripheral Opioid Antagonists and Rotation Therapy

Opioid rotation may be indicated because of ineffectiveness/toxicity of initial opioid

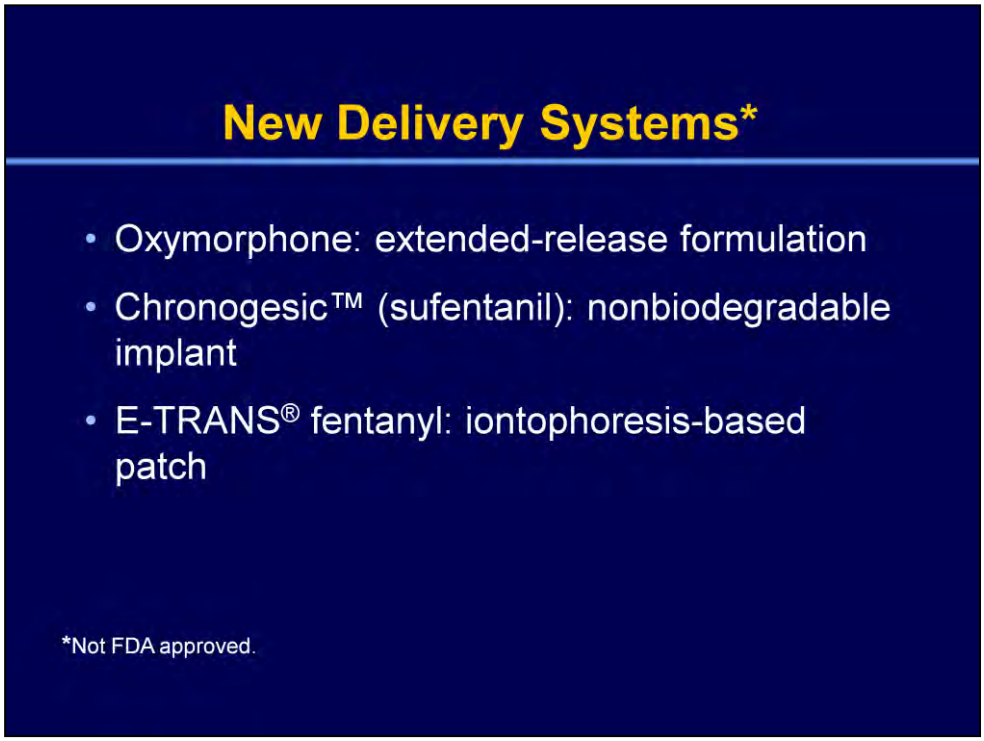
- If indicated, opioid rotation therapy should be approached carefully, particularly in patients with incomplete cross-tolerance. Conservative dose-conversion ratios are advisable
- Peripheral opioid antagonists are an emerging approach for opioid side effects, particularly constipation

- A typical chart review of patients with chronic noncancer pain found that the first opioid prescribed was effective for just 36% of patients, and was stopped for side effects in 30%, and for ineffectiveness in 34% of patients.[1]
- Many patients show wide-ranging sensitivities to opioids, both with regard to analgesic activity and side effects. Moreover, patients may also develop tolerance to an agent after repeated administration. Patients tolerant to one agent will often demonstrate cross-tolerance to another; however, this cross-tolerance is often incomplete. While the relative potencies of opiates have been reasonably well established in naïve patients, these potencies are not accurate in tolerant patients. Therefore, switching agents in patients highly tolerant to a specific mu-opioid agonist may lead to serious problems.[2] In patients with incomplete cross-tolerance, a 30%–50% reduction in "equianalgesic dose" is advisable—supplemented as necessary by prn breakthrough pain analgesic dosing—until optimal dose of the long-acting analgesic has been determined.
- Peripheral opioid antagonists have been shown to mediate, modulate, or reduce such opioid-related side effects as nausea, vomiting, constipation, and pruritus.[3,4]

1. Quang-Cantagrel ND, Wallace, MS, Magnuson SK. Opioid substitution to improve the effectiveness of chronic noncancer pain control: a chart review. *Anesth Analg*. 2000;90:933-937.
2. Pasternak GW. Insights into mu opioid pharmacology: The role of mu opioid receptor

subtypes. *Life Sci*. 2001;68:2213-2219.

3. Schmidt WK. Almivopan (ADL 8-2698) is a novel peripheral opioid antagonist. *Am J Surg*. 2001;182(5A Suppl):27S-38S.
4. Friedman JD, Dello Buono FA. Opioid antagonists in the treatment of opioid-induced constipation and pruritus. *Ann Pharmacother*. 2001;35:85-91.



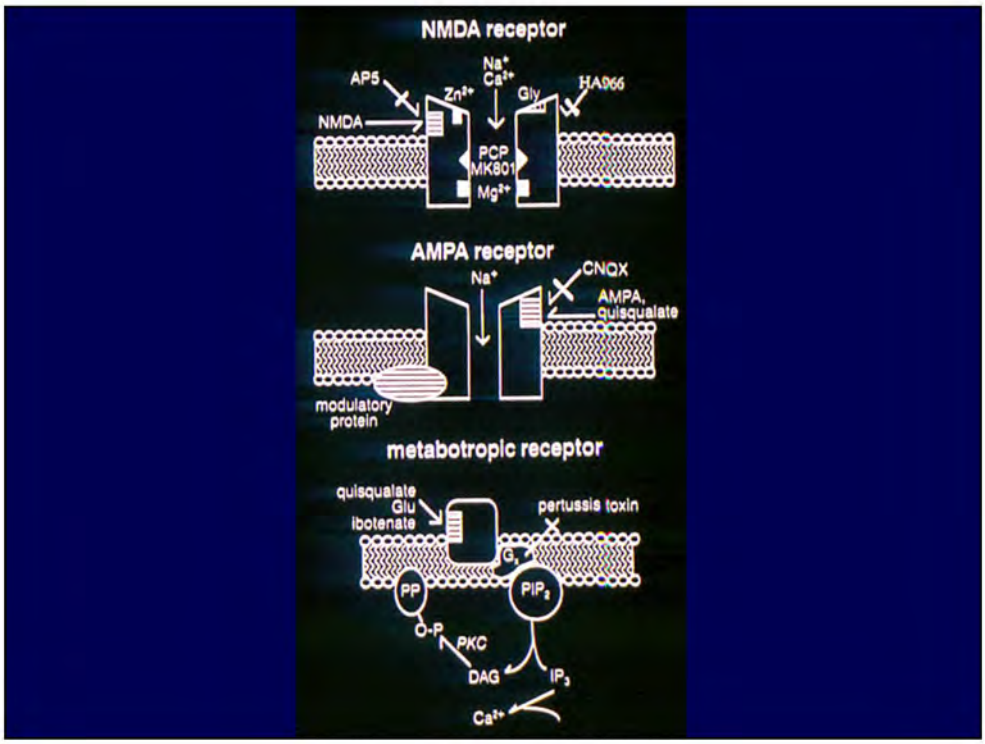
- Oxymorphone, an opioid analgesic, has been available as an injection (1 mg/ml) or as a rectal suppository (5 mg). Recently, there have been several investigational trials of an extended-release tablet formulation, including a multicenter, placebo-controlled, randomized, double-blind parallel study in patients with mild-to-moderate osteoarthritis pain.
- Chronogesic™, in Phase III trials, employs sufentanil, a fentanyl analog, in a DUROS® implant. A nonbiodegradable, osmotically driven titanium cylinder is implanted in the body. Water from surrounding tissues enters one end of the cylinder through a semipermeable membrane. This causes the osmotic engine inside the cylinder to release the therapeutic agent at a controlled rate. Chronogesic is designed to provide three months of systemic continuous pain relief for patients with opioid-responsive malignant and nonmalignant chronic pain.[2]
- E-TRANS® fentanyl, in development, is an electrotransport system that allows self-titration of the therapeutic agent in patients with acute pain. E-TRANS is designed to deliver agents that normally would not diffuse across the skin. A small electric current passes through the patient's skin, between two electrodes on the patch. Charged molecules of the agent are attracted to the electrode of the opposite polarity. E-TRANS technology is potentially useful in delivering rapid boluses of a drug on demand.[3]

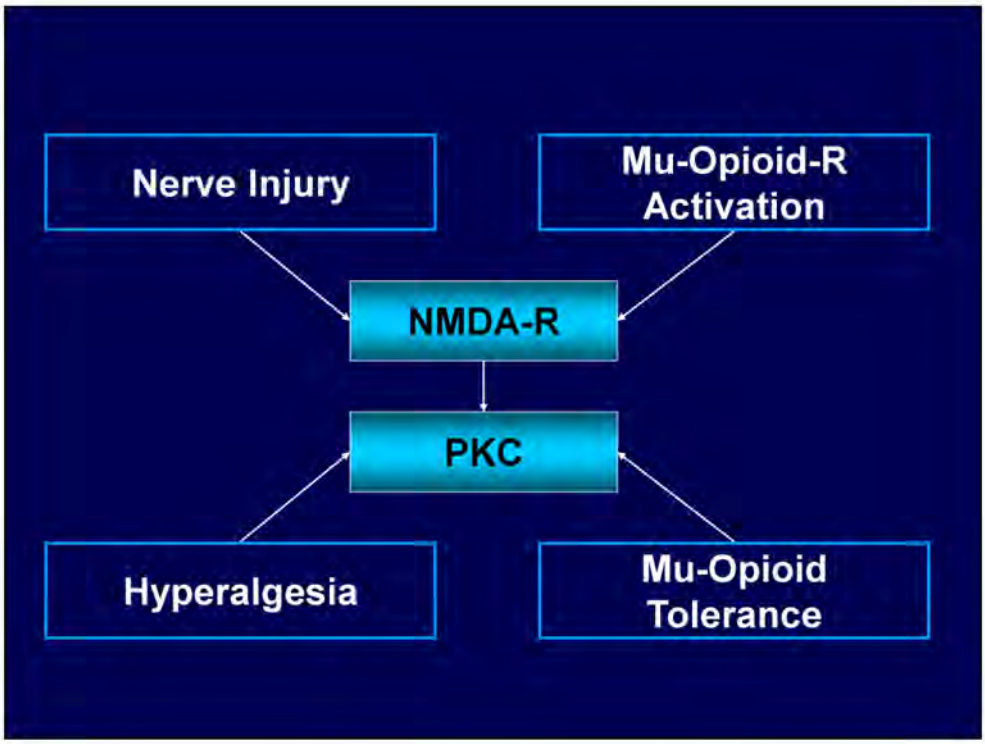
1. Hussain MA, Aungst BJ. Intranasal absorption of oxymorphone. *J Pharm Sci*. 1997;86:975-976.

2. CHRONOGESIC™ Pain Therapy System. Available at: http://www.Durect.com. Accessed December 18, 2002.
3. Mystakidou K. E-TRANS fentanyl. ALZA. *Current Opin Invest Drugs*. 2002;3:463-469.

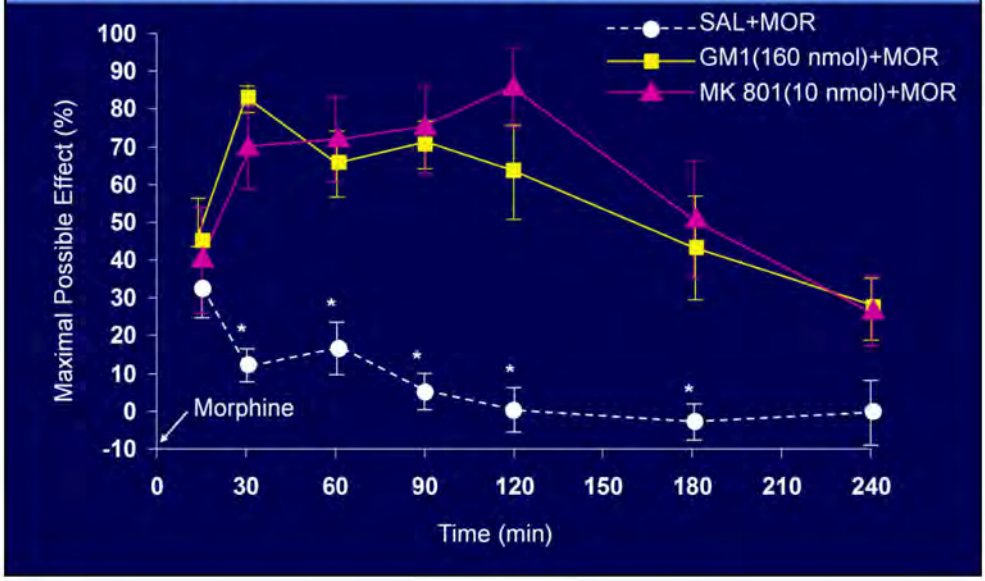
Interactions Between Opioid Tolerance/Pathological Pain

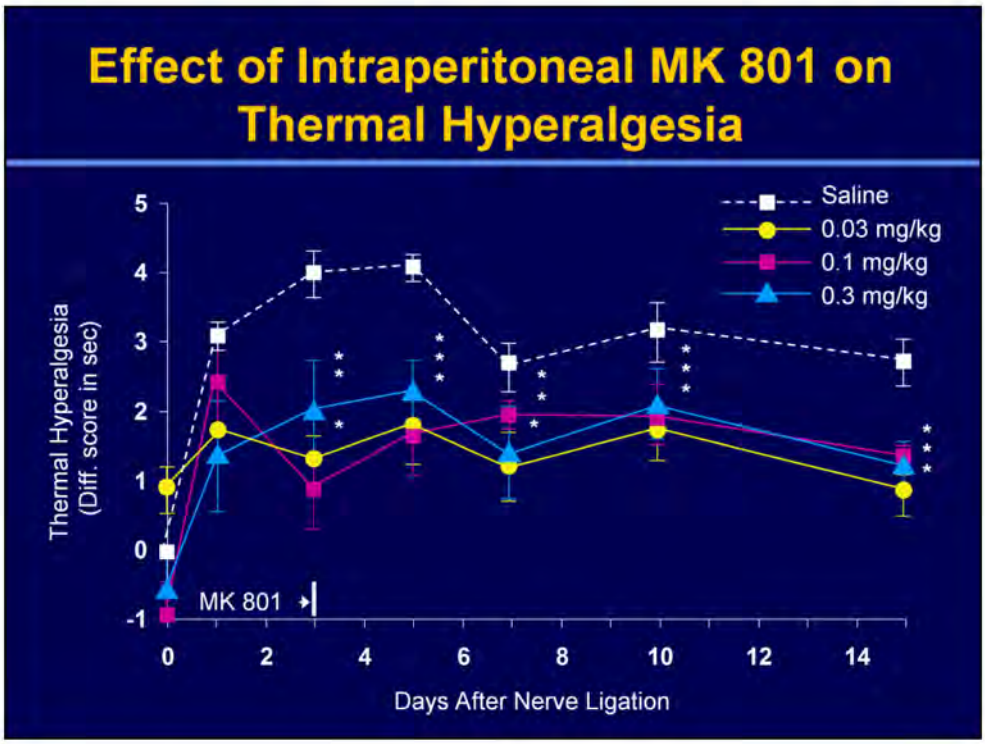
- Evidence for common mechanisms involving tolerance and pathological pain
  - NMDA receptor
  - Protein kinase C
- Clinical implications

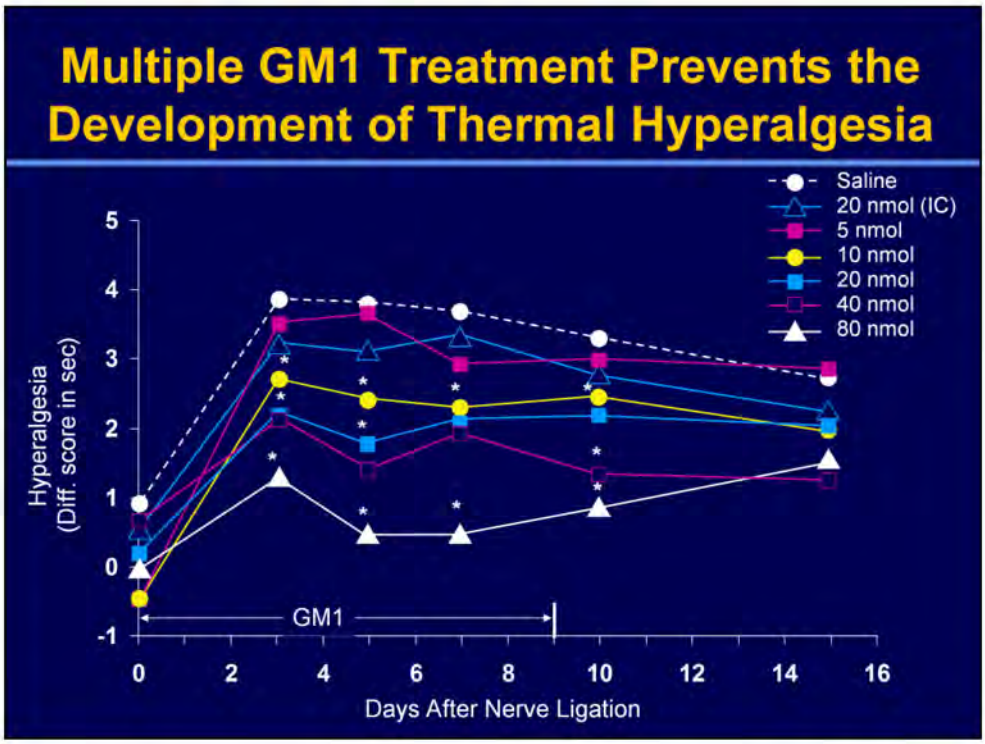

NMDA receptor
AP5
NMDA
Na+
Ca2+
Zn2+
Gly
HA966
PCP
MK801
Mg2+
AMPA receptor
Na+
CNQX
AMPA,
quisqualate
modulatory
protein
metabotropic receptor
quisqualate
Glu
ibotenate
pertussis toxin
PP
PIP2
O-P
PKC
DAG
IP3
Ca2+

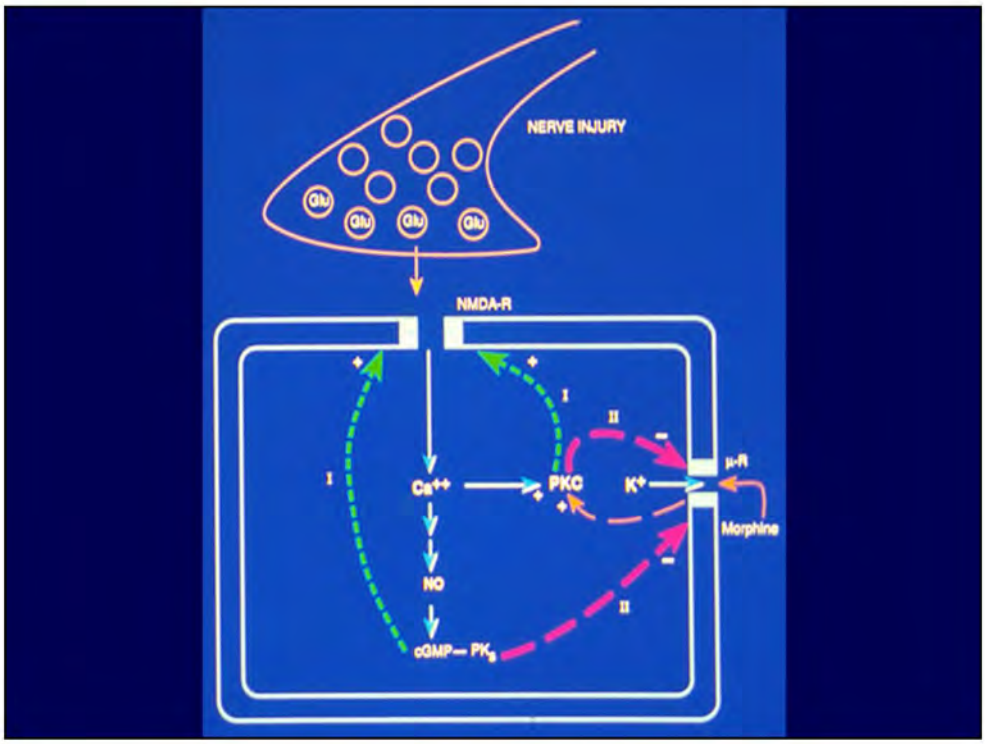


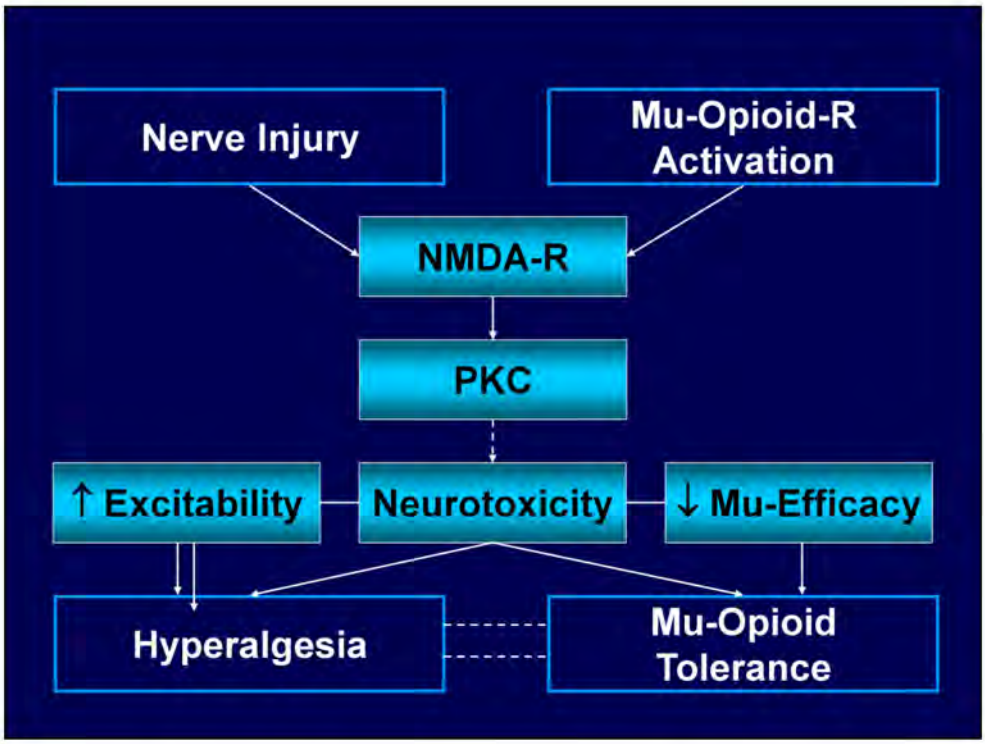
Intrathecal GM1 or MK 801 Blocks the Development of Morphine Tolerance





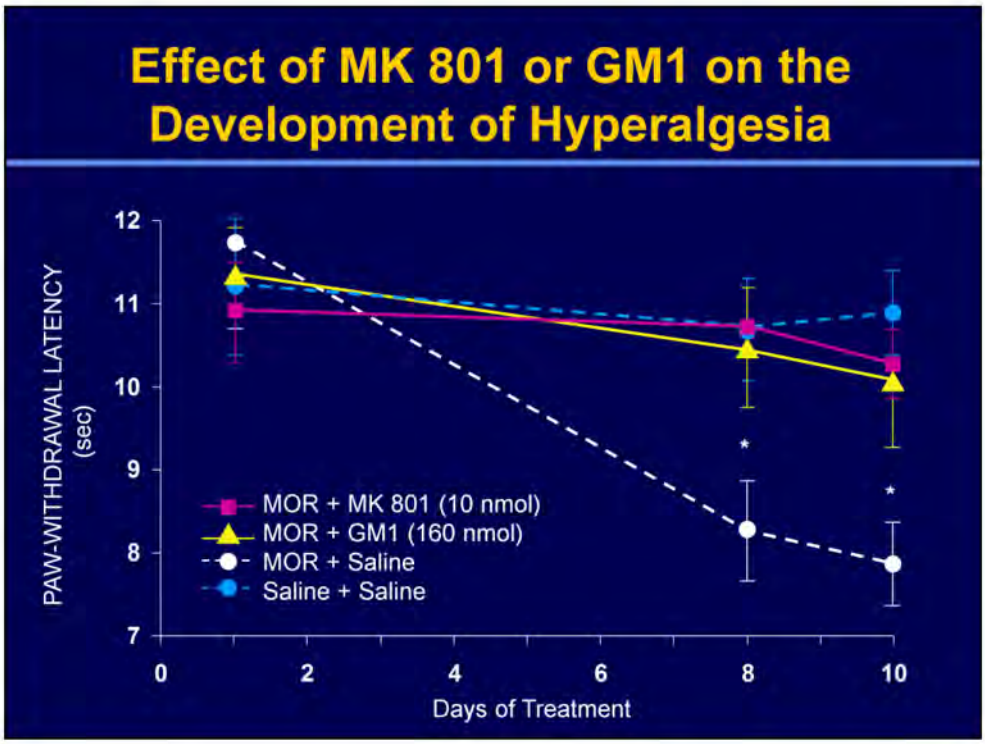

Multiple GM1 Treatment Prevents the Development of Thermal Hyperalgesia
Saline
20 nmol (IC)
5 nmol
10 nmol
20 nmol
40 nmol
80 nmol
Hyperalgesia (Diff. score in sec)
5
4
3
2
1
0
-1
GM1
0
2
4
6
8
10
12
14
16
Days After Nerve Ligation


NERVE INJURY
Glu
Glu
Glu
Glu
NMDA-R
I
II
I
Ca++
PKC
K+
μ-R
Morphine
NO
II
cGMP— PK


Nerve Injury
Mu-Opioid-R Activation
NMDA-R
PKC
↑ Excitability
Neurotoxicity
↓ Mu-Efficacy
Hyperalgesia
Mu-Opioid Tolerance

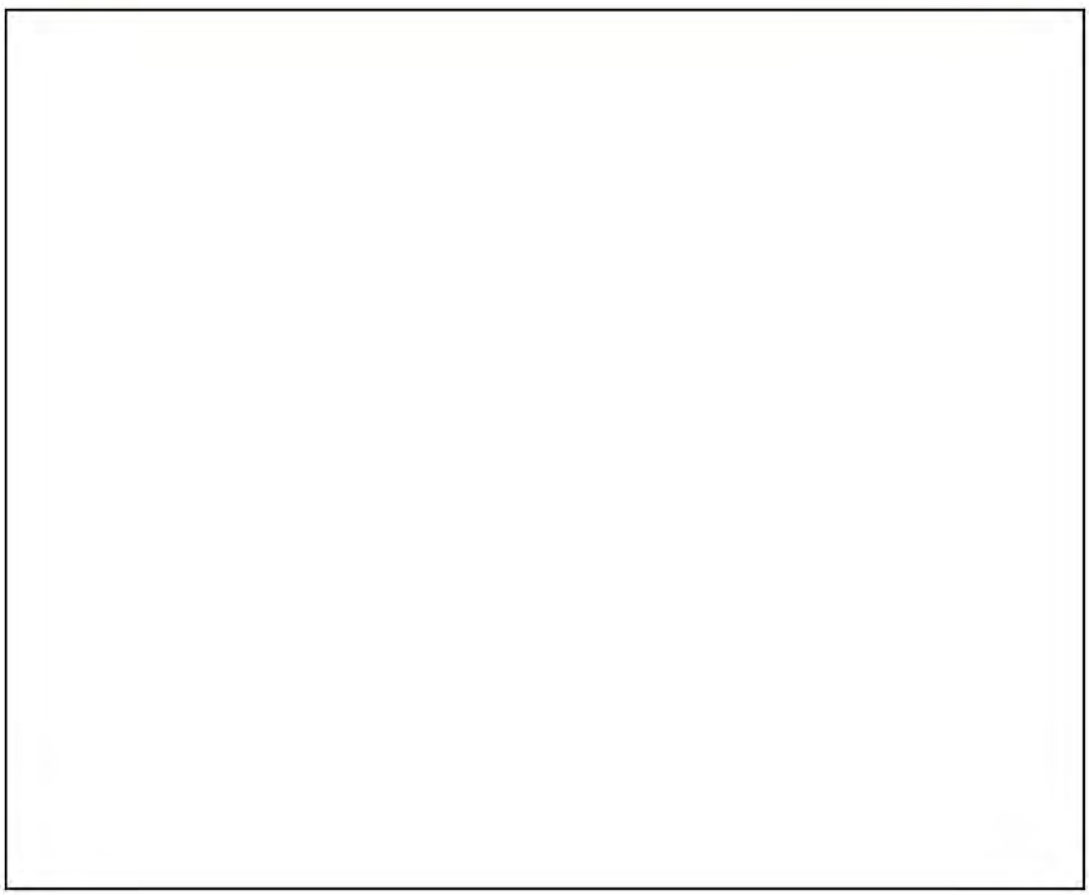
Repeated Opioid Exposure → A Pathological Pain State

A Pathological Pain State → Decreased Opioid Effectiveness


Effect of MK 801 or GM1 on the Development of Hyperalgesia
PAW-WITHDRAWAL LATENCY (sec)
12
11
10
9
8
7
0
2
4
6
8
10
Days of Treatment
MOR + MK 801 (10 nmol)
MOR + GM1 (160 nmol)
MOR + Saline
Saline + Saline
*
*

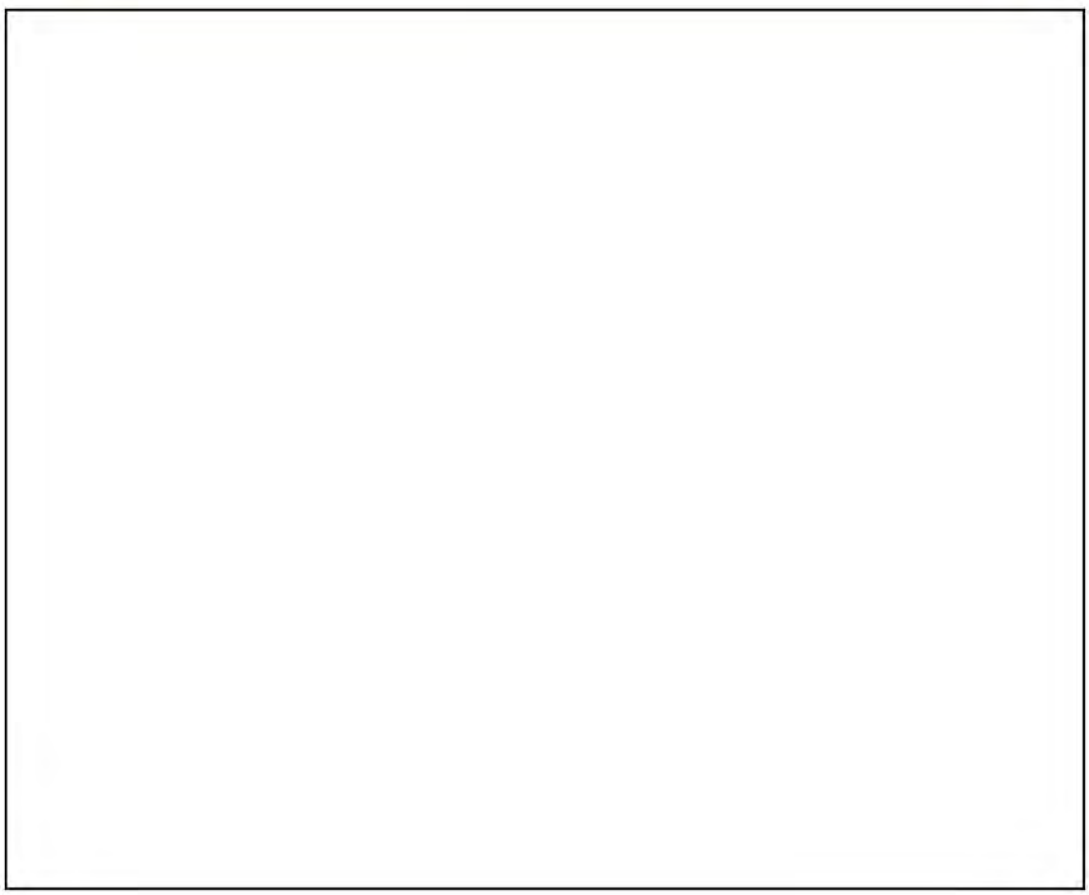
Clinical Implications: Opioid Treatment → Hyperalgesia

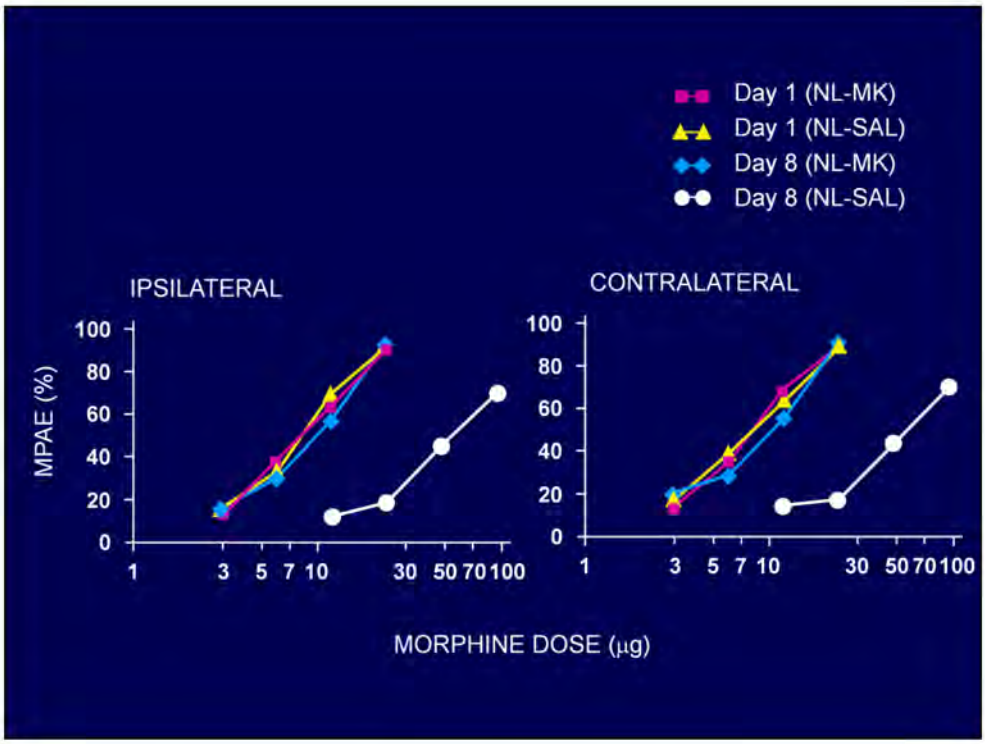
- Exacerbating preexisting pain
- Counteracting opioid analgesia
- Confounding treatment outcome
- Leading to potential CNS damage—irreparable?



Clinical Evidence: Opioid Treatment → Hyperalgesia

- Hyperalgesia induced by spinal sufentanil or morphine infusion
- Hyperalgesia and increased opioid use following intraoperative remifentanil infusion
- Hyperalgesia and allodynia in cancer pain patients receiving IV morphine
- Methadone maintenance subjects



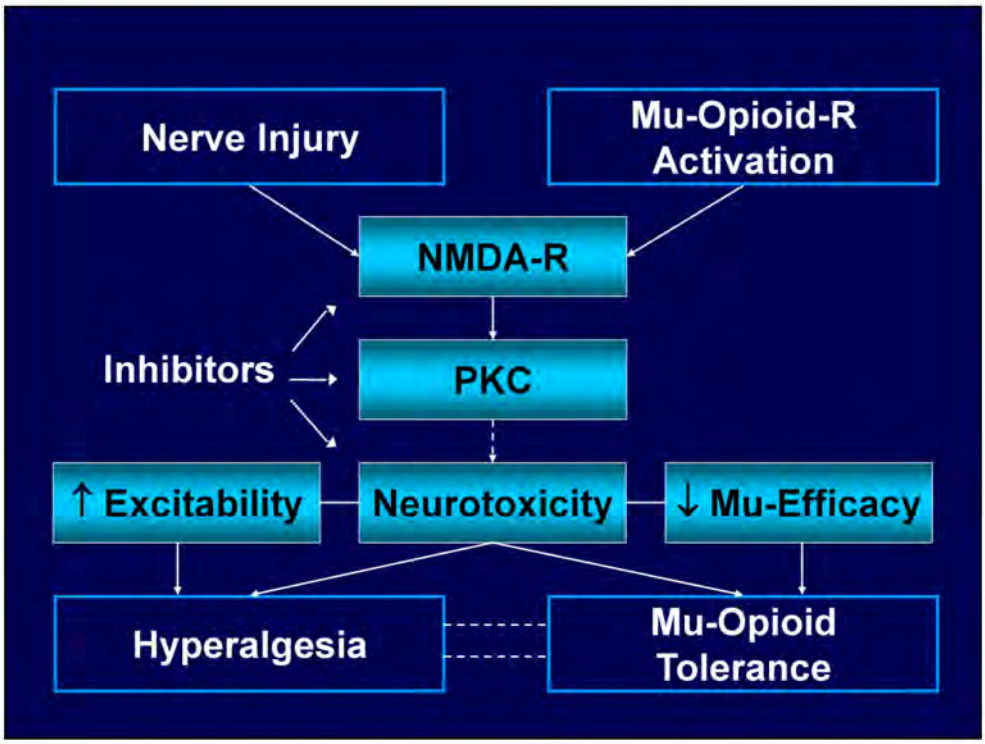

Day 1 (NL-MK)
Day 1 (NL-SAL)
Day 8 (NL-MK)
Day 8 (NL-SAL)
IPSILATERAL
CONTRALATERAL
MPAE (%)
100
80
60
40
20
0
1
3
5
7
10
30
50
70
100
MORPHINE DOSE (μg)

Clinical Implications: Hyperalgesia → Tolerance

- A potential mechanism relating to the reduced opioid efficacy in pathological pain treatment
- A confounding factor in the assessment of treatment outcomes
  - Opioid tolerance?
  - Progress of the original pain state?
  - Both?

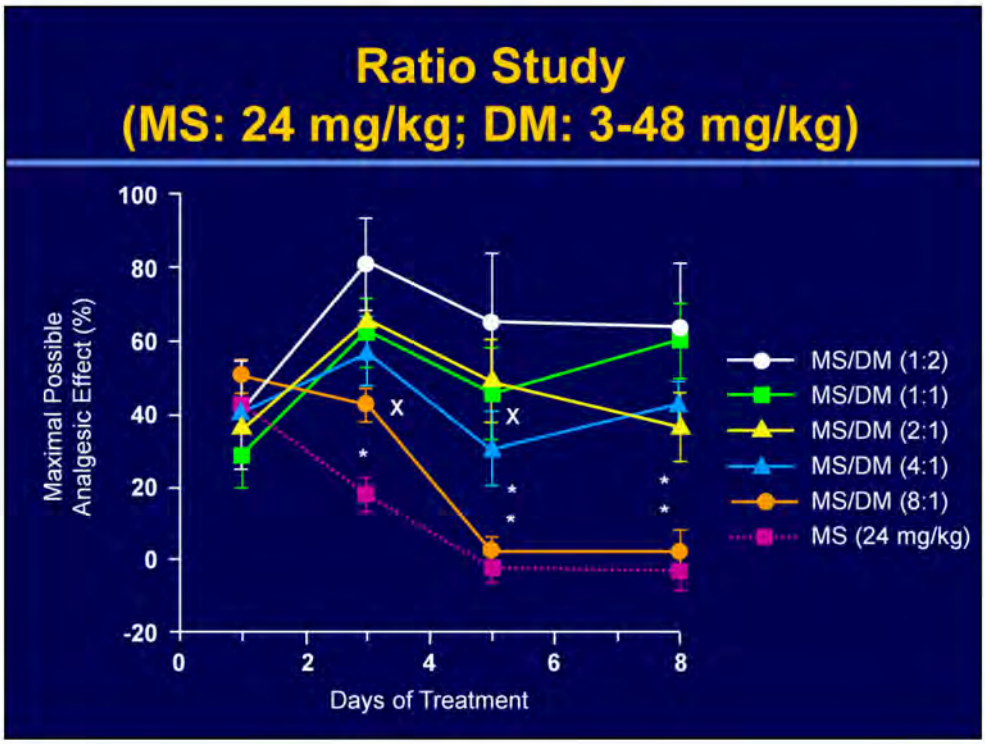
Clinical Evidence: Reduced Opioid Efficacy in Pathological Pain Treatment

- Common clinical experience
- Often not used as the first-line choice
- Inconsistent clinical data and lack of well-controlled clinical studies
- Increased initial doses and speedy dose escalations?


Nerve Injury
Mu-Opioid-R Activation
NMDA-R
Inhibitors
PKC
↑ Excitability
Neurotoxicity
↓ Mu-Efficacy
Hyperalgesia
Mu-Opioid Tolerance

Drugs With Potential NMDA-R Antagonist Property

- Dextromethorphan
- Ketamine
- Methadone (*d*-Methadone)
- Amantadine (Memantine)
- Amitriptyline (TCAs?)
- Thiopental
- Demerol?


Ratio Study
(MS: 24 mg/kg; DM: 3-48 mg/kg)
Maximal Possible Analgesic Effect (%)
100
80
60
40
20
0
-20
0
2
4
6
8
Days of Treatment
MS/DM (1:2)
MS/DM (1:1)
MS/DM (2:1)
MS/DM (4:1)
MS/DM (8:1)
MS (24 mg/kg)